Factor XI: A new target for anticoagulation?

Dr. Marcello Di Nisio

University G. D'Annunzio , Chieti-Pescara, Italy

Disclosures for Dr. Di Nisio

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Consultant	No relevant conflicts of interest to declare
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	Daiichi Sankyo, Mylan
Scientific Advisory Board	LeoPharma, Janssen

Outline

- Limitations of current anticoagulant treatments
- Role of FXI in hemostasis, thrombosis, and CAT
- Preclinical and epidemiological evidence supporting FXI as a safer target than FXa
- Clinical studies with FXI inhibitors
- Reversal agents and interference with coagulation assays
- Conclusions and future directions

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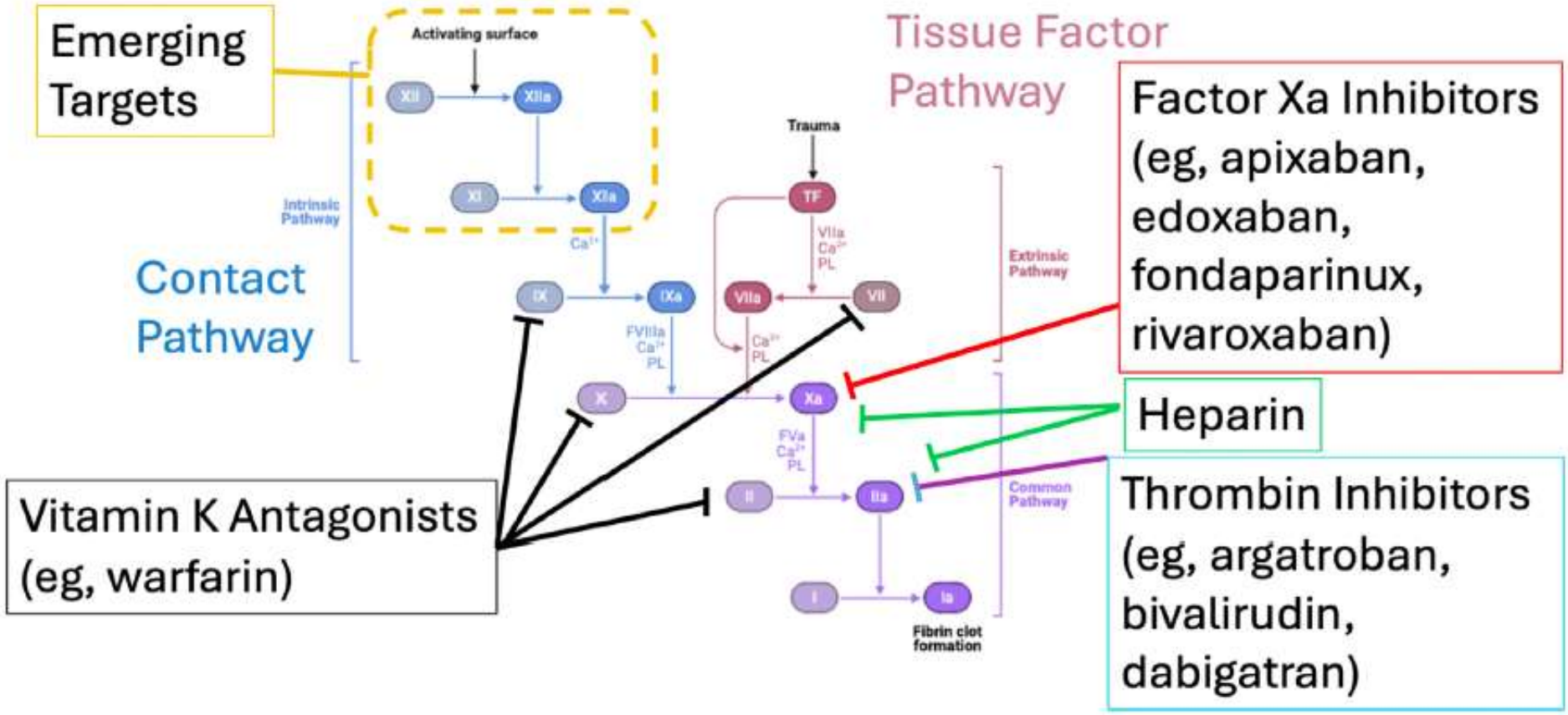
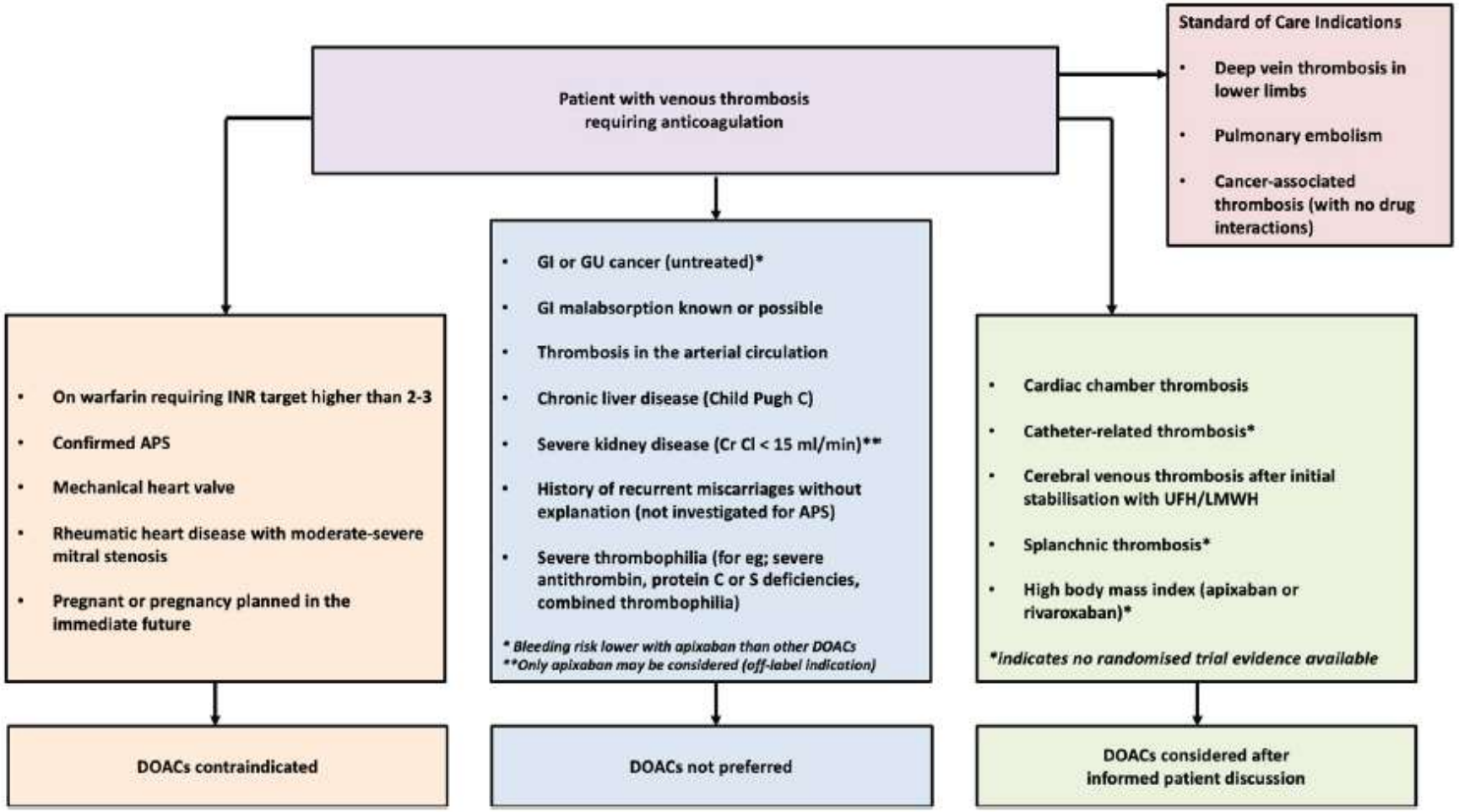


Barnes GD. JTH 2025

Vitamin K antagonists	LMWH	Factor Xa inhibitors
Oral	Daily sc injections	Oral
No renal clearance	Renal clearance	Renal and hepatic clearance
Possible DDIs	No interaction with chemotherapy	Possible DDIs
Problems with GI absorption: vomiting, diarrhea, GI surgery, mucosal defects	No intestinal absorption	Problems with GI absorption: vomiting, diarrhea, upper gastrointestinal surgery, mucosal defects
Food interactions	No food interactions	No food interactions

DOACs failure in patients with VTE —why and what next?



Swan D, et al. JTH 2025

Direct oral anticoagulant failure in patients with VTE—why and what next?

Non adherence

Factors associated with nonadherence	Factors that may improve adherence
Forgetfulness	Provision of pill boxes or blister packs
Twice daily dosing	Alarms prompting medication administration
Patient belief that anticoagulation is not required	Reassurance of the requirement for a DOAC from a physician/specialist
Financial burden of medication costs	Provision of free medication
Fear of DOAC-related bleeding	Awareness of the availability of reversal agents
Younger age	Laboratory tests to confirm drug activity
Male gender	Regular follow-up
Shift work	

Non aderence up to 30%

Dose prescribing errors 5-37%

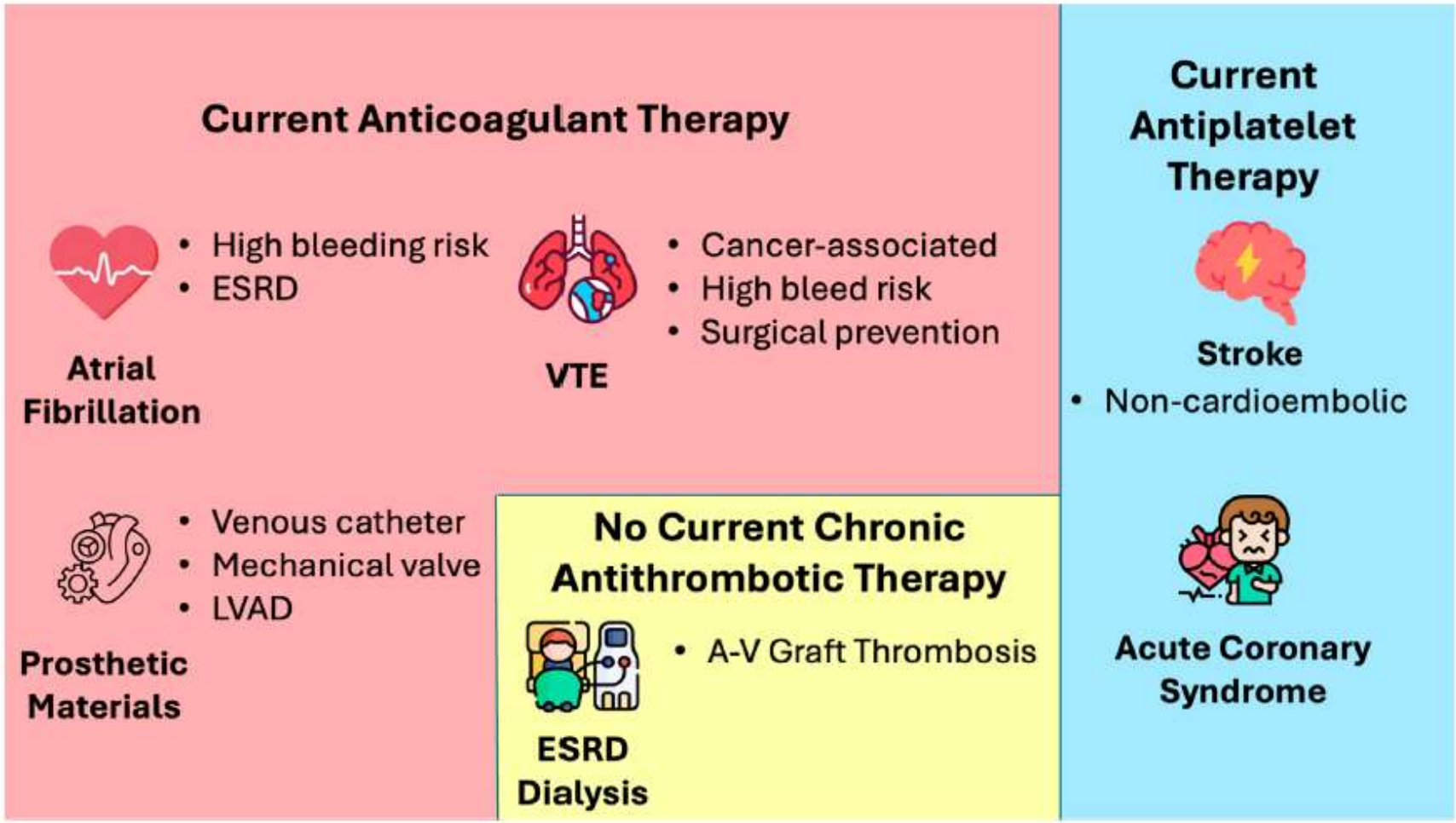
Swan D, et al. JTH 2025

Potentially altered absorption following GI surgery and in pts with malabsorption: warfarin is usually favored

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
GBS/total gastrectomy	?⇩ Adequate peak/trough plasma levels in 2/2 patients after gastrectomy Minimal impact on apixaban pharmacokinetics was seen in 14 patients following GBS No VTE in a retrospective review of 20 patients after GBS	?⇩ Significantly reduced up to 56% (pharmacokinetic studies) Adequate peak/trough plasma levels in 3/4 patients after gastrectomy One VTE in retrospective review of 32 patients after GBS Reduced peak/trough in 5/7 patients after GBS No significant impact on prophylactic dose rivaroxaban in 6 patients after GBS	?⇩ Adequate peak plasma levels but undetectable trough levels in 2/2 patients after total gastrectomy Possibly reduced due to pH-dependent absorption	⇩ Thrombosis and reduced peak/trough levels in 2/2 patients after total gastrectomy, and in 2/2 patients after GBS
Partial/SG	☑ Adequate peak/trough plasma levels in 2/2 patients after partial gastrectomy and minimal impact on apixaban pharmacokinetics seen in 14 patients following SG No VTE in a retrospective review of 18 patients after SG	?⇩ Adequate levels in 1/1 patient after SG No VTE in a retrospective review of 20 patients after SG No significant impact on prophylactic dose rivaroxaban in 6 patients after SG	?⇩ No data but adequate peak in total gastrectomy Requires plasma level monitoring	?⇩ No data Reduced in total gastrectomy
Gastric banding	☑ No VTE in retrospective review of 4 patients	?⇩ No VTE in retrospective review of 8 patients Caution due to required calorific intake of 15 mg and 20 mg doses	?⇩ No data but adequate peak in total gastrectomy Requires plasma level monitoring	?⇩ No data Reduced in total gastrectomy
Small bowel resection/short bowel syndrome	⇩ Requires plasma level monitoring and personalized dosing	⇩ Requires plasma level monitoring and personalized dosing	☑ No studies available Pharmacokinetic potential for absorption suggests likely clinical efficacy (requires plasma level monitoring)	☒ Indirect evidence of inadequate plasma concentration—use not recommended
Large bowel resection (total/subtotal colectomy)	?⇩ Evidence of reduced plasma concentration in 1 case	☑ Evidence of sufficient plasma concentration in 4 cases	☑ No studies available, colon not involved in absorption	☑ No studies available, colon not involved in absorption

☑: likely clinical efficacy; ?⇩: possible reduced efficacy; ⇩: reduced efficacy demonstrated; ☒: inadequate efficacy demonstrated.

Swan D, et al. JTH 2025

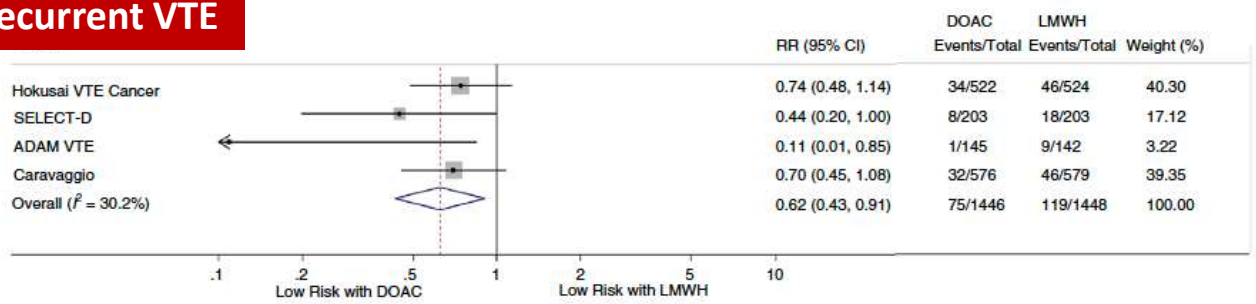


RED treated primarily with anticoagulants, but high bleeding risk
BLUE managed with antiplatelets, but residual thromboembolic risk
YELLOW not managed with any chronic antithrombotic therapy

Barnes GD. JTH 2025

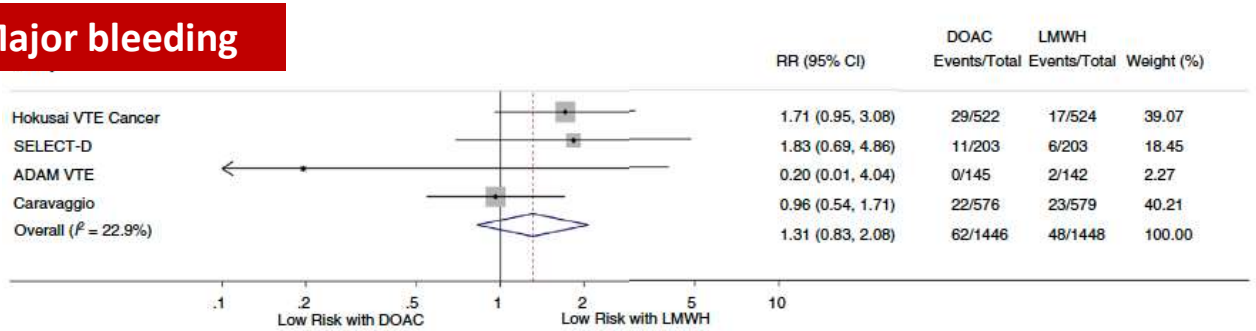
Bleeding remains the major concern with both oral FXa inhibitors and LMWH

Recurrent VTE



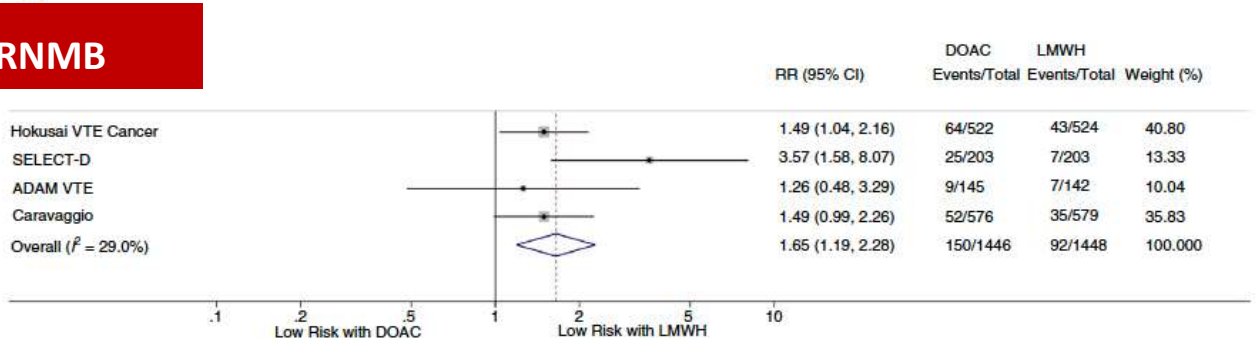
5.2% vs 8.2%

Major bleeding



4.3% vs 3.3%

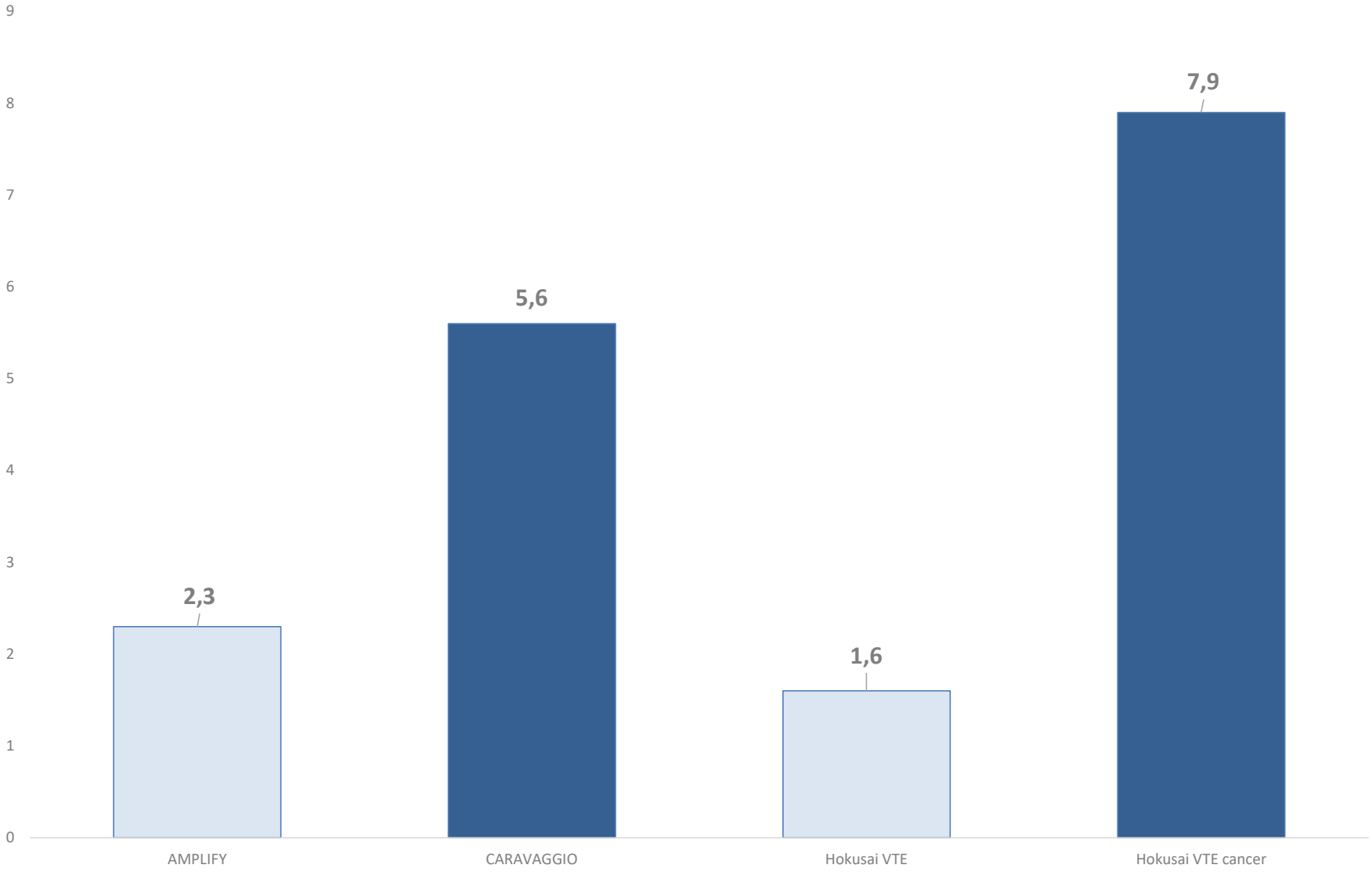
CRNMB



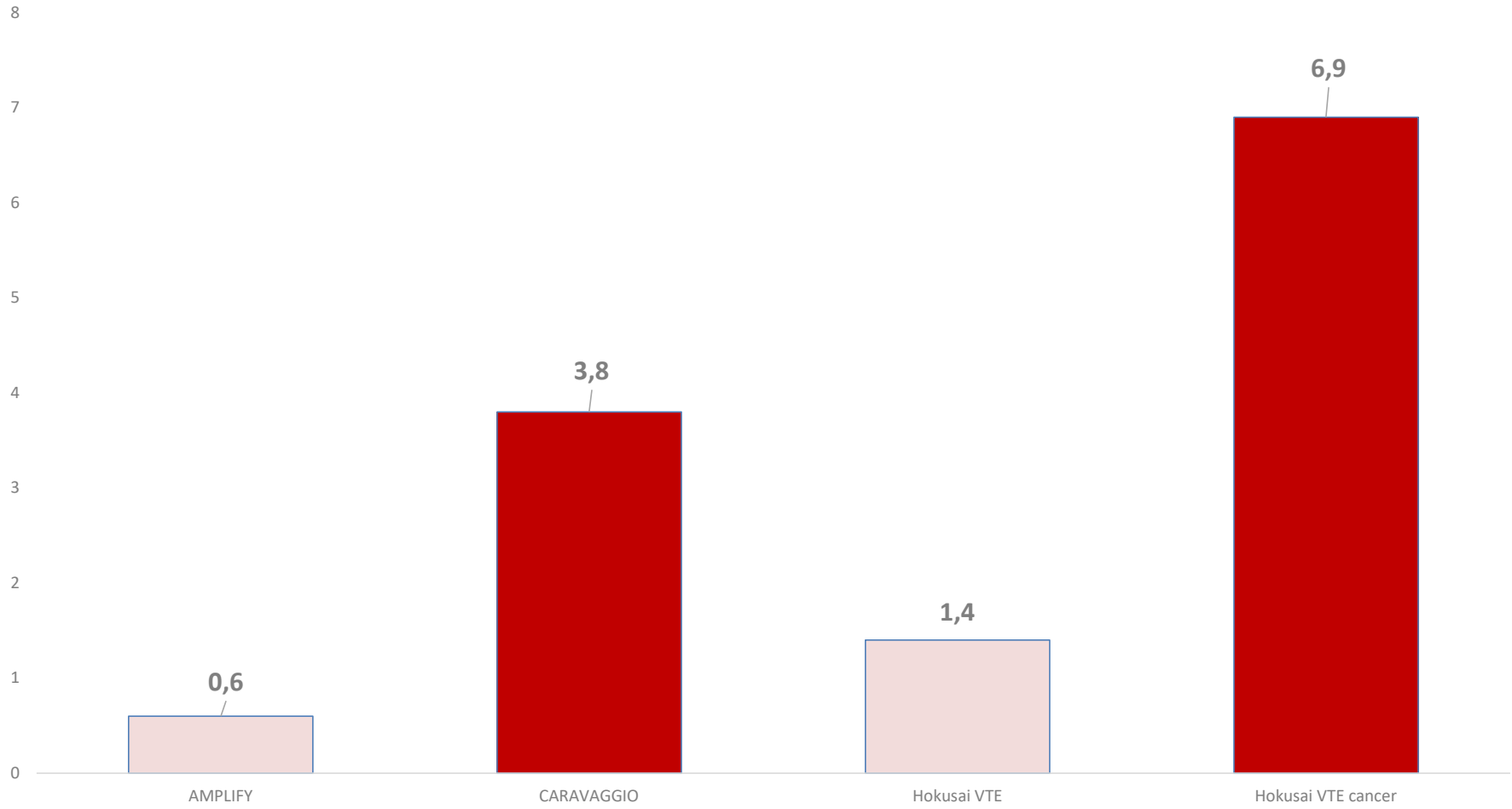
10.4% vs 6.4%

Moik F, et al. RPTH 2020

Recurrent VTE with DOACs in patients with or without active cancer



Major bleeding with DOACs in patients with or without active cancer



Risk of bleeding with current anticoagulant strategies

Risk of bleeding on anticoagulants remains non-negligible, in particular in:

- Cancer patients
- Elderly patients with comorbidities
- Patients with renal or liver insufficiency
- Patients with history of bleeding or major bleeding risk factors
- Patients requiring concomitant antiplatelet treatment

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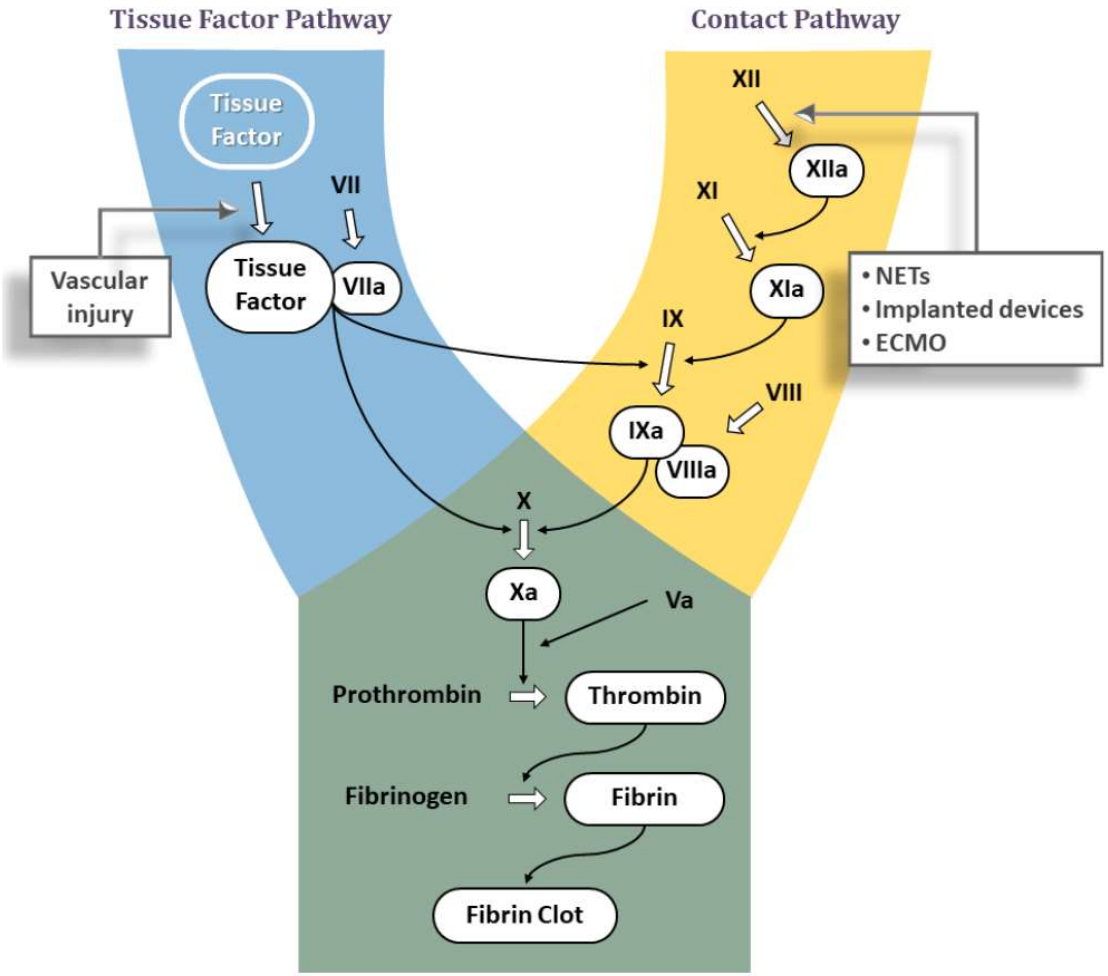
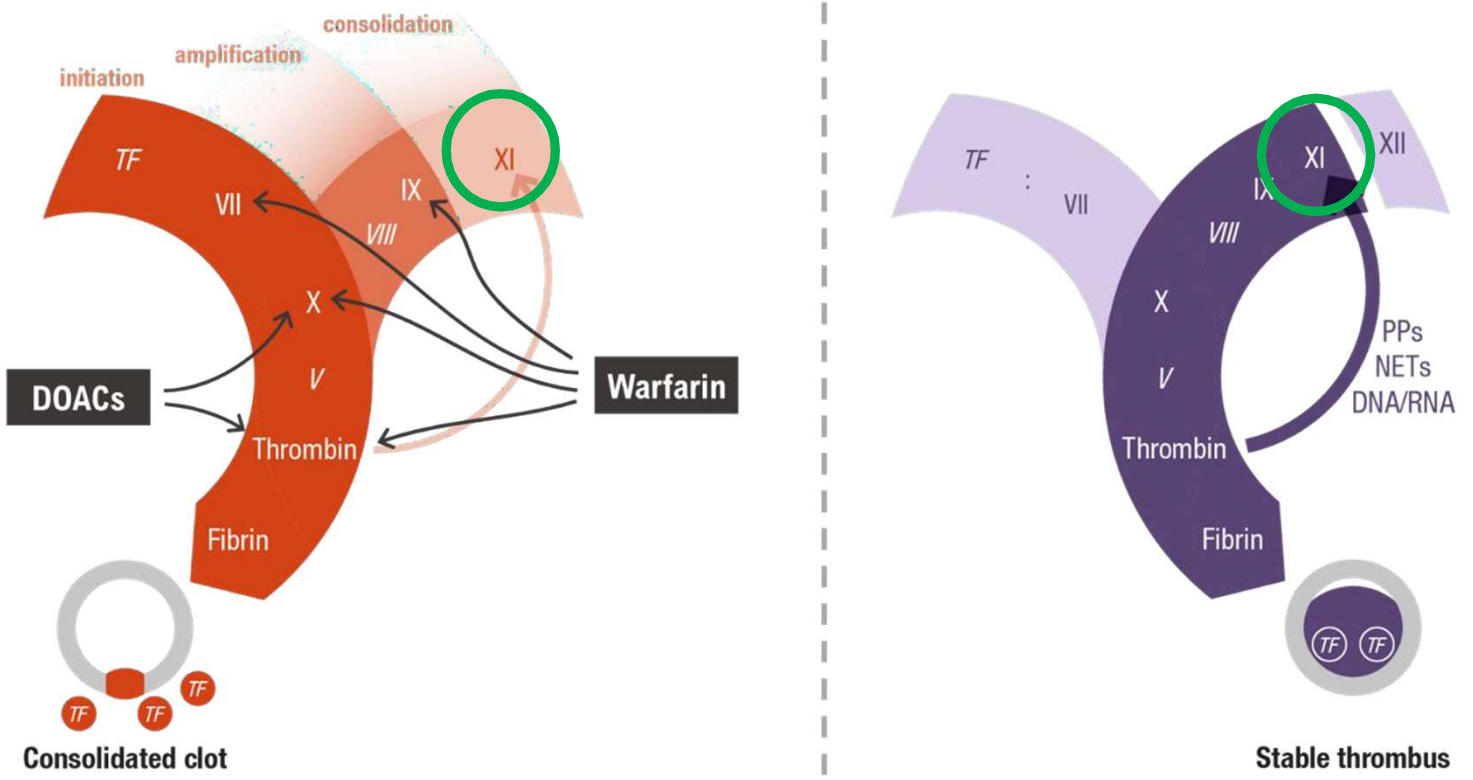
The classic model of the coagulation cascade



Badimon JJ, et al. J Cardioivasc Develop Dis 2022

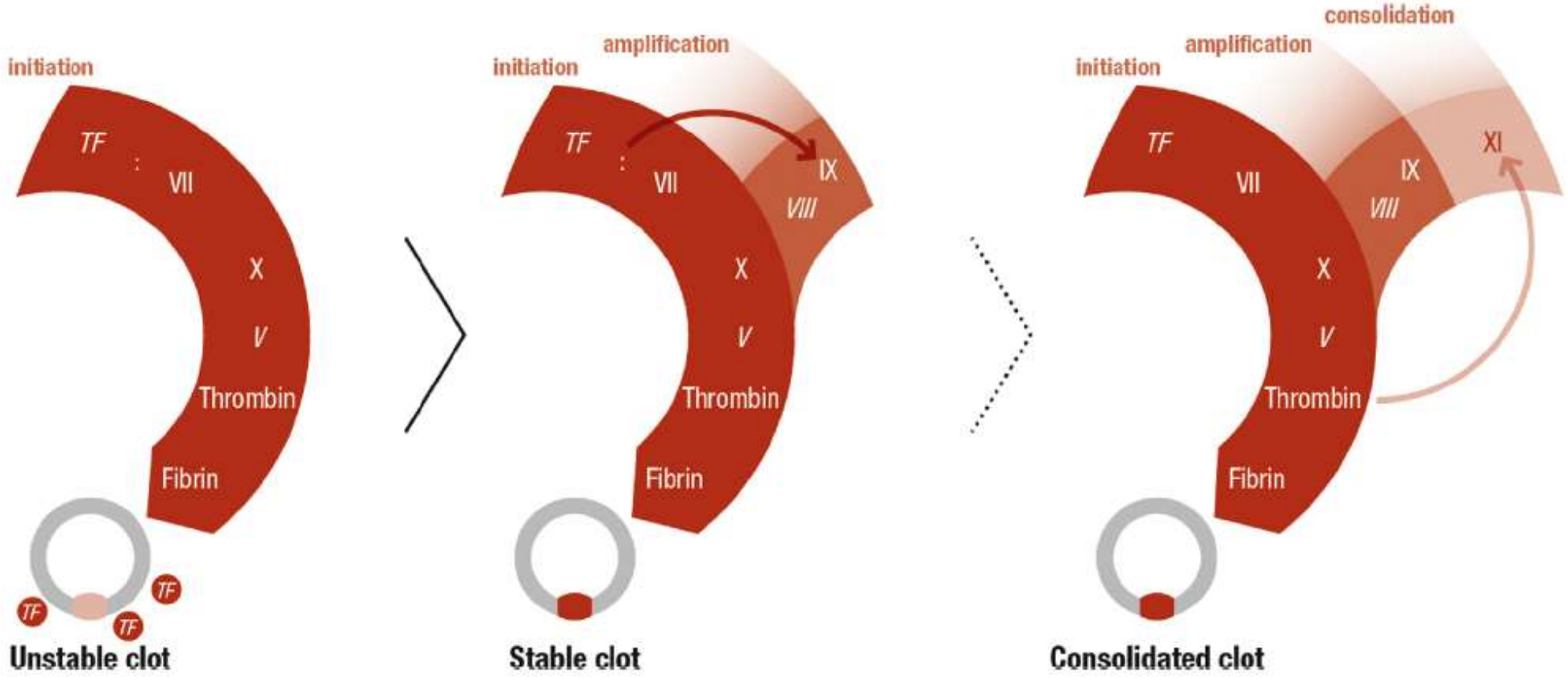
FXI Inhibition may offer safer anticoagulation

Potential to Uncouple Hemostasis from Thrombosis



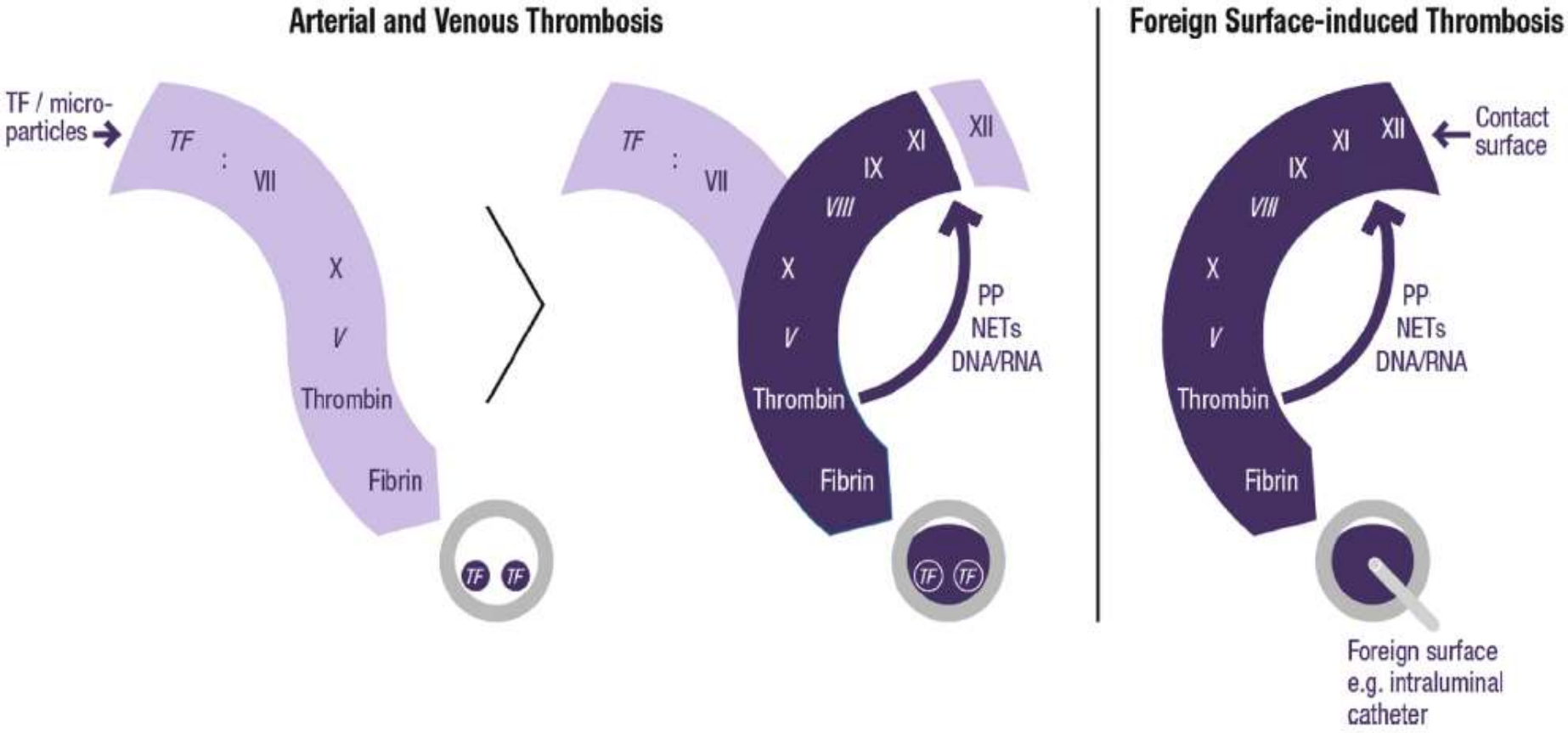
Hsu C, et al. *JAm Coll Cardiol* 2021;78:625-631

Processes required for hemostasis



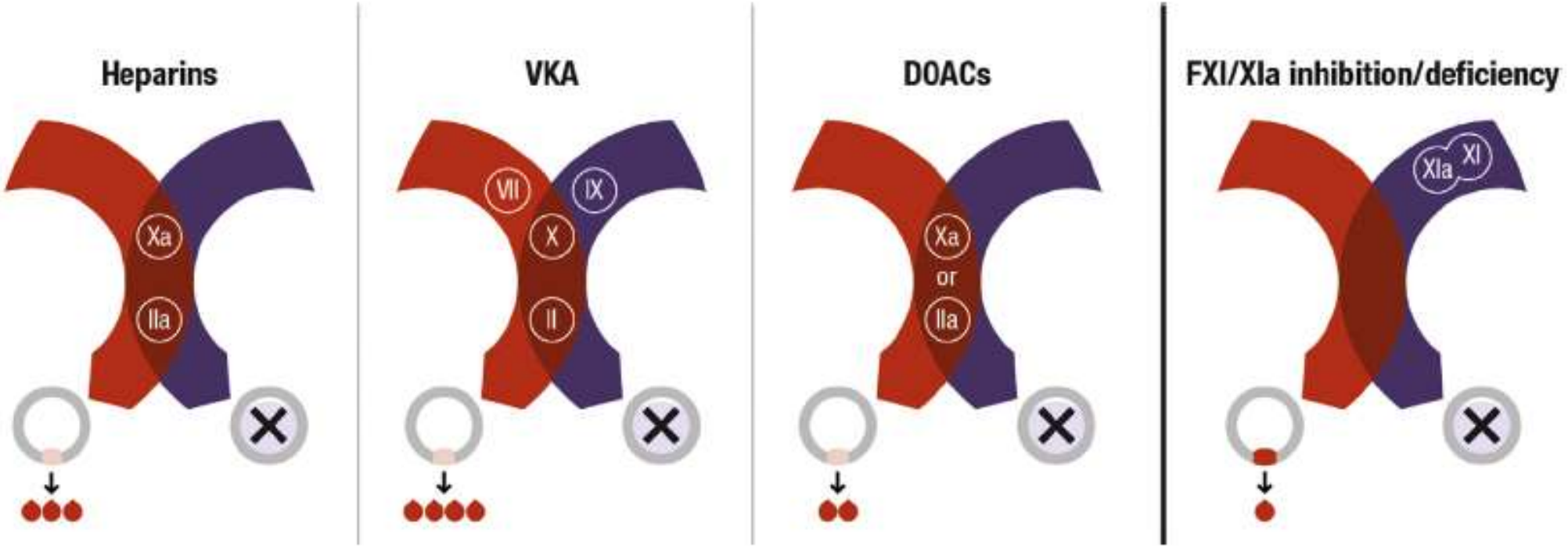
Hsu C, et al. JACC 2021

Processes that contribute to thrombosis



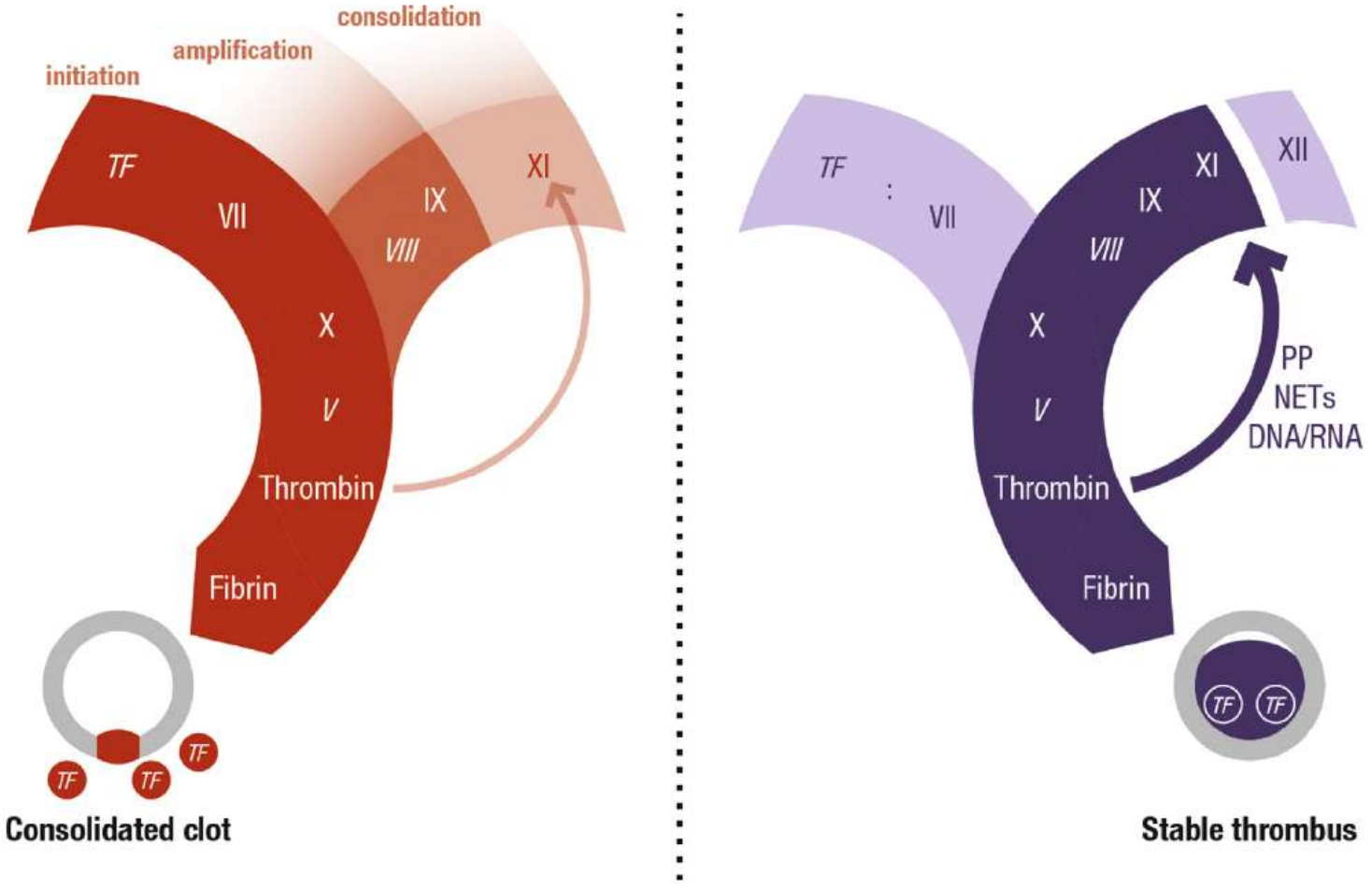
Hsu C, et al. JACC 2021

Impact of various anticoagulants on hemostasis versus thrombosis

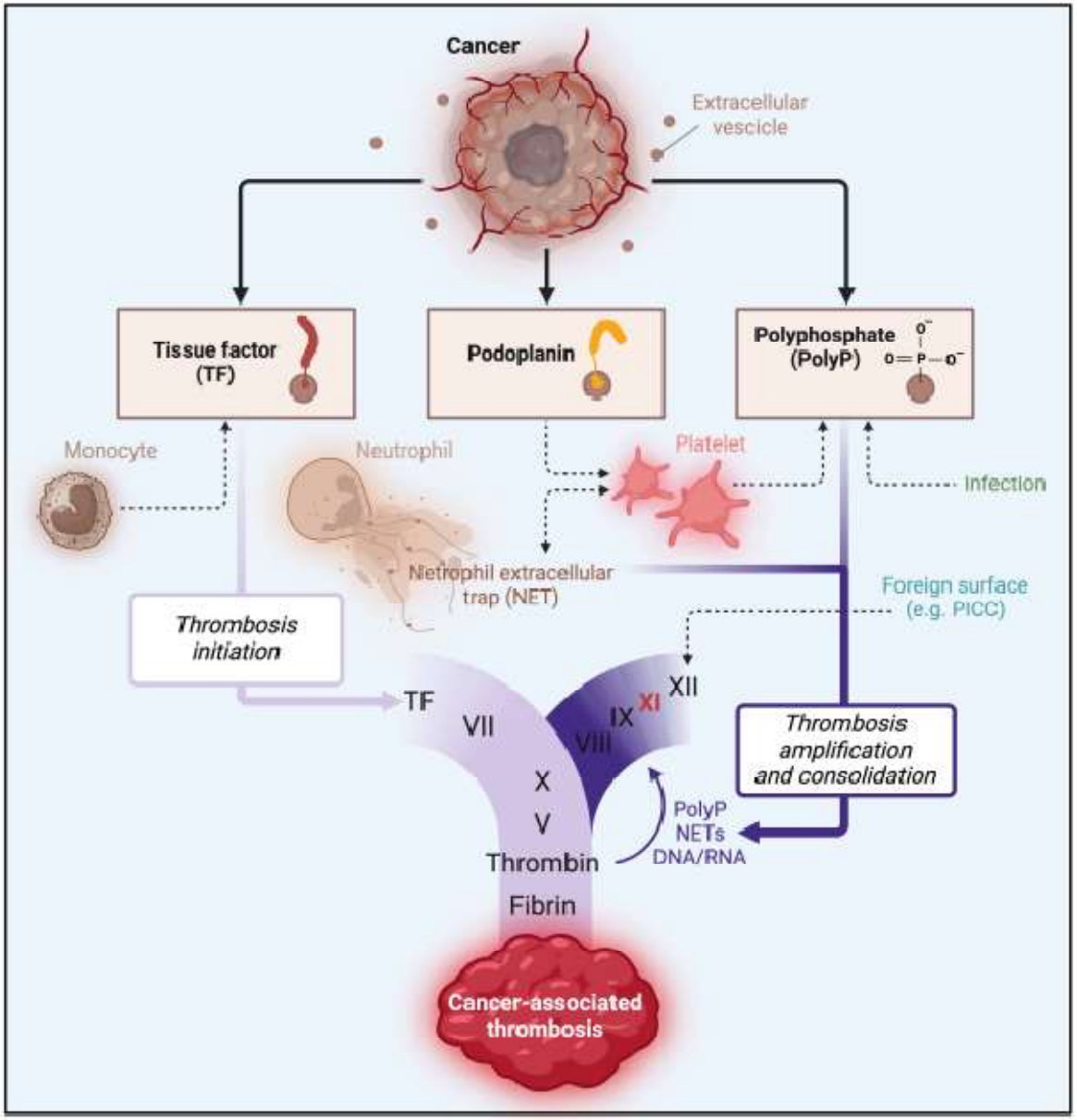


Hsu C, et al. JACC 2021

Factor XI inhibition to uncouple thrombosis from hemostasis

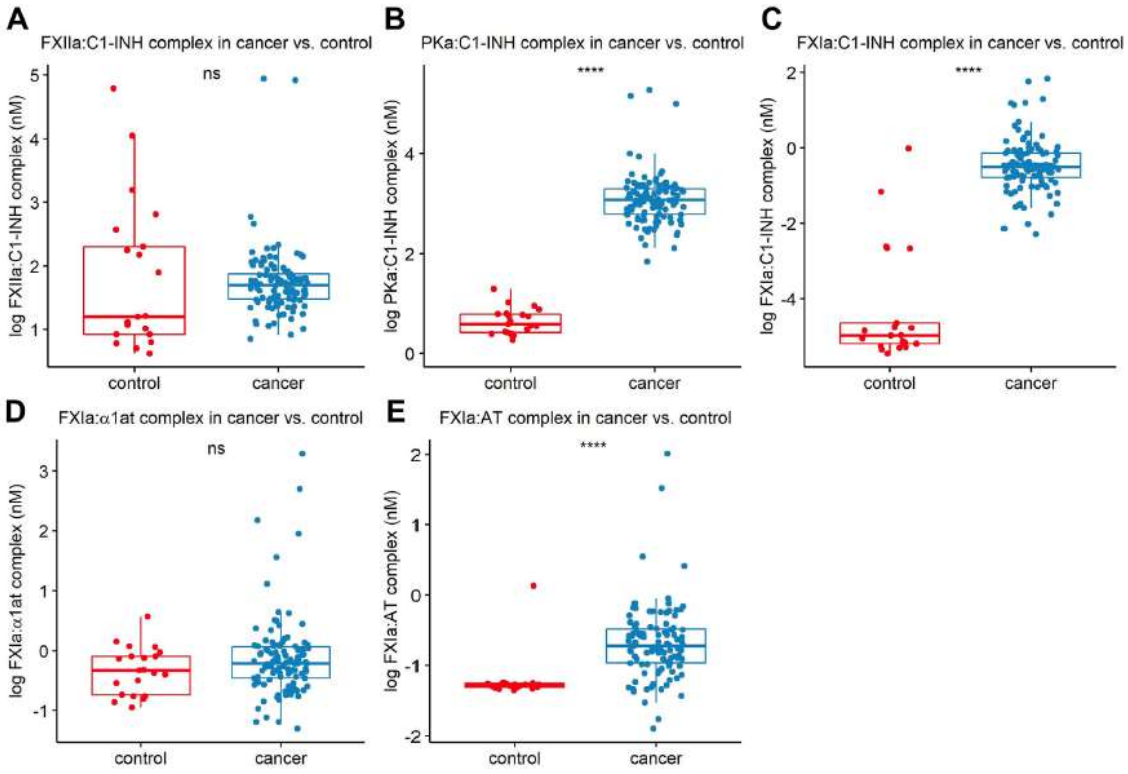


Hsu C, et al. JACC 2021



Di Nisio M, et al. BTVB 2024

Contact system and intrinsic pathway activation in patients with advanced pancreatic cancer: a prospective cohort study



The contact system and intrinsic pathway activation are increased in patients with pancreatic cancer

Bosch FTM, et al. JTH 2023

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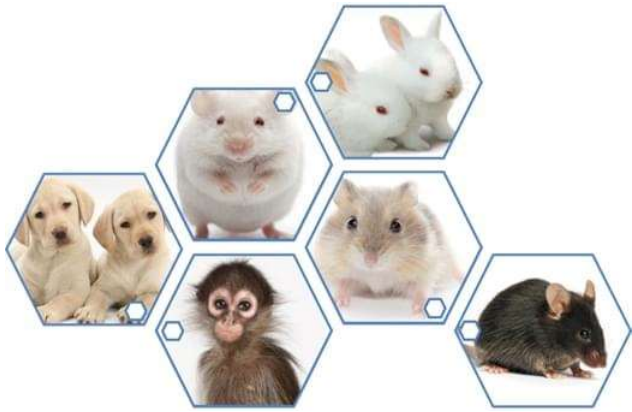
Pre-clinical animal studies



Mice deficient in FXI or FXII: defective thrombus formation at sites of arterial or venous injury without increased bleeding

Wang X. J Thromb Haemost. 2005; Wang X. J Thromb Haemost. 2006; Ay C. J Thromb Haemost. 2017; Schumacher WA. Eur J Pharmacol. 2007; Revenko AS. Blood. 2011;Renné . J Exp Med. 2005; Renné T. J Thromb Haemost. 2009; Grover SP. Arterioscler Thromb Vasc Biol. 2019

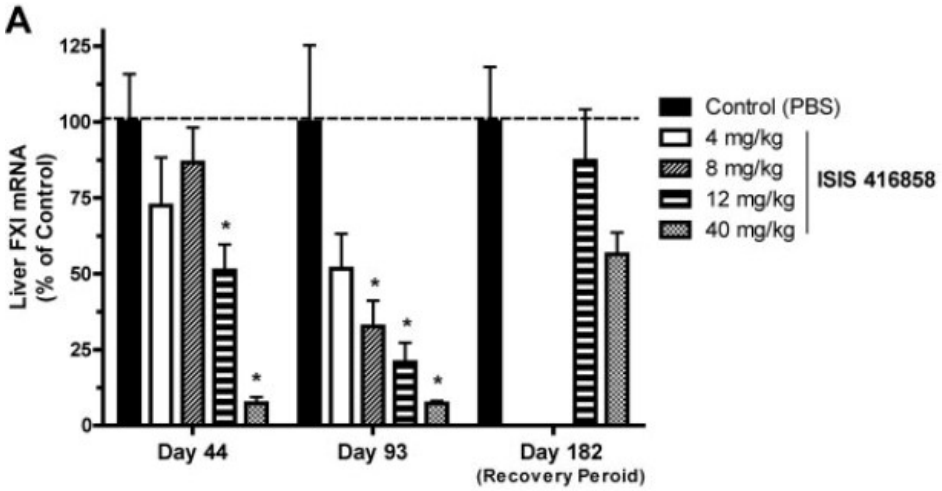
Ab against FXI inhibited thrombosis in rodent models without affecting bleeding, and FXI knock down with ASOs reduced shunt thrombosis in baboons and catheter-related thrombosis in rabbits

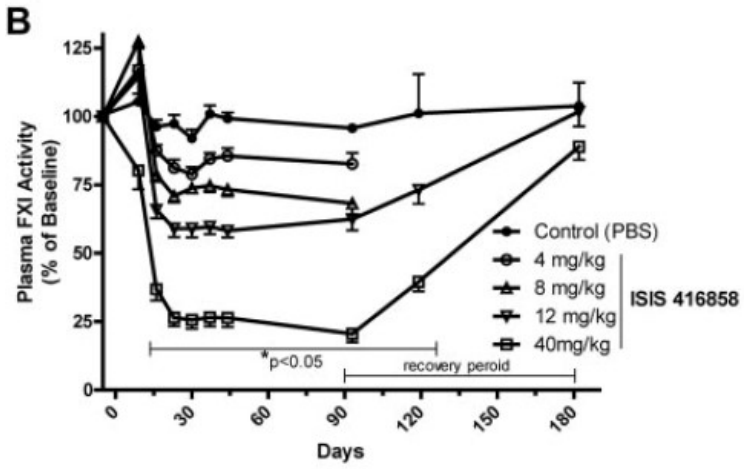
Grover SP. Arterioscler Thromb Vasc Biol. 2019

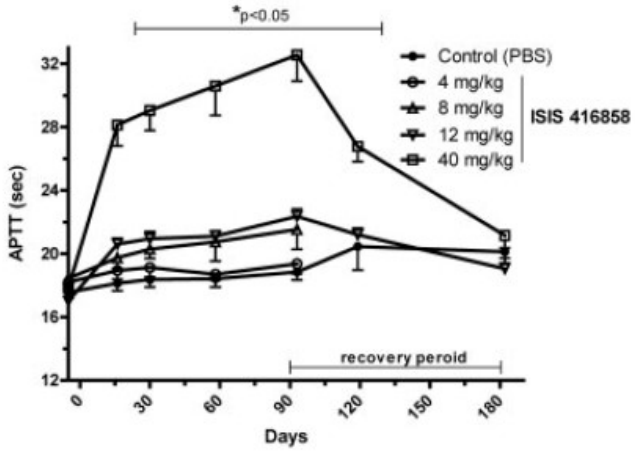
More potent antithrombotic effects with FXI- than FXII-directed Ab in monkeys

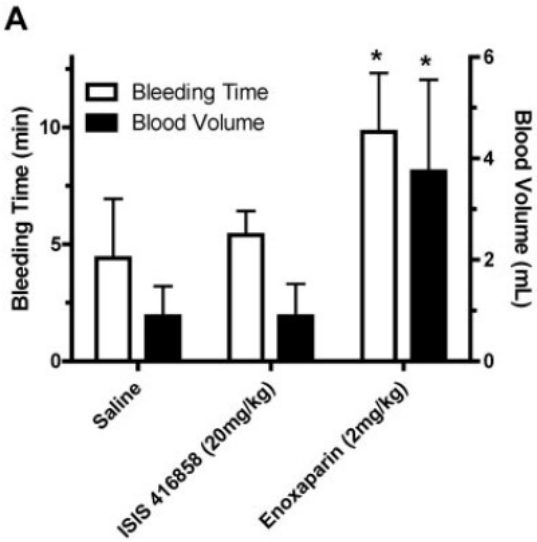
Younis HS. Blood. 2012; Matafonov A. Blood. 2014; Gruber A. Blood. 2003

ASO inhibition of FXI prolongs APTT without increased bleeding risk in monkeys





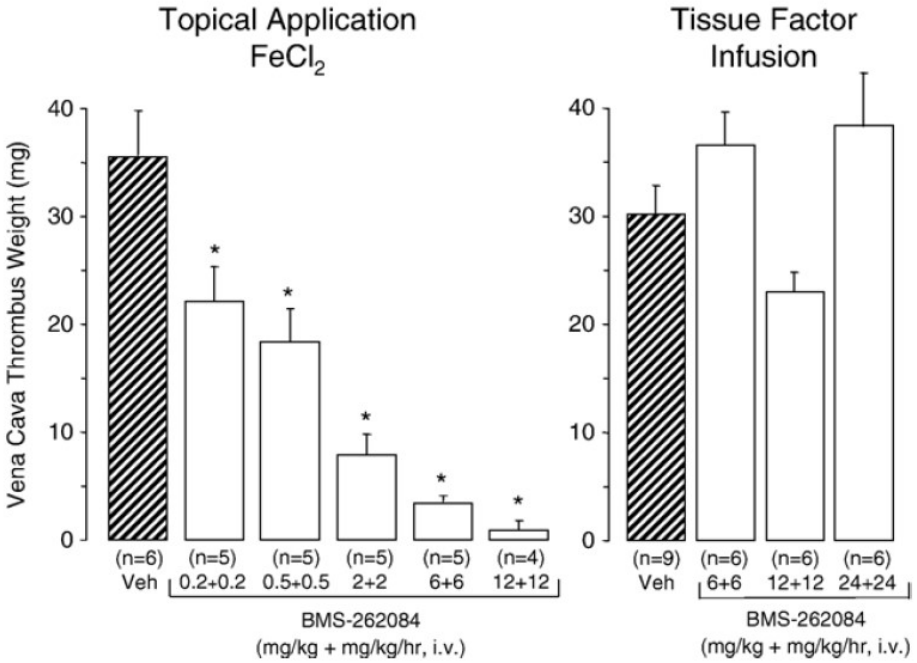




Younis HS, et al. Blood 2011

Rat models of thrombosis and hemostasis

BMS-262084 irreversible and selective small molecule inhibitor of FXIa

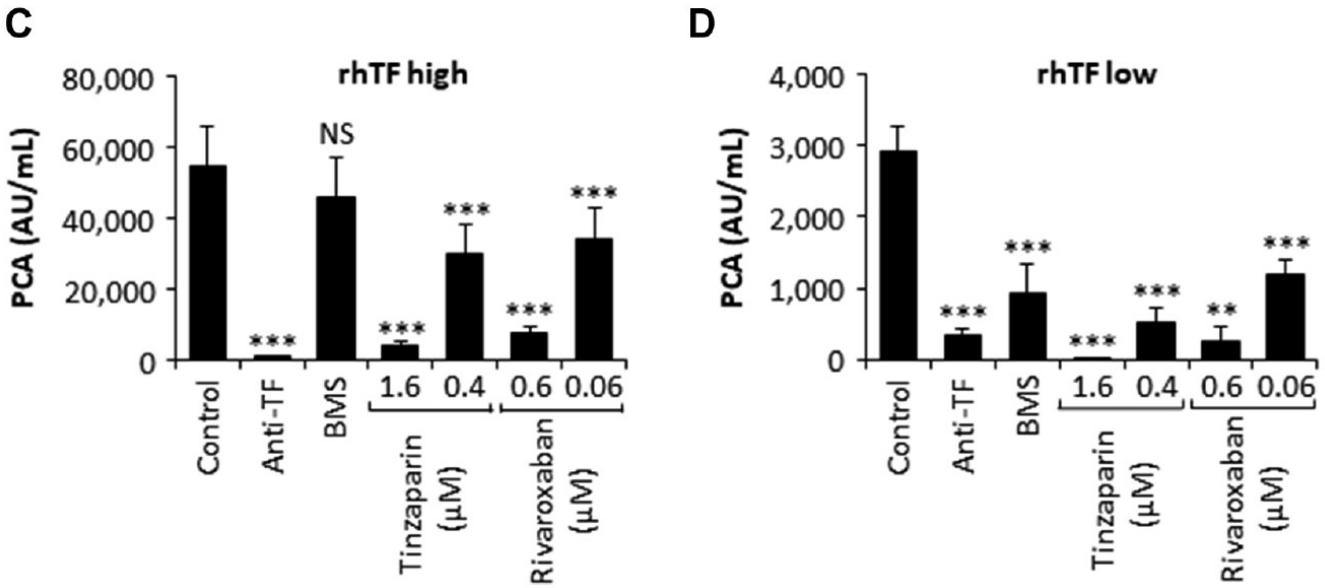


No effect on TF-induced DVT

Schumacher WA, et al. Eur J Pharmacol 2007

Effect of FXI inhibition on tumor cell-induced coagulation activation

Procoagulant activity of 4 TF-expressing tumor cell lines analyzed by single-stage clotting and thrombin generation assay



BMS-262084 inhibits TF-induced coagulation only at low TF concentrations

Mader J, et al. J Thromb Haemost 2023

Factor XI deficiency (Hemophilia C)

- Prevalence 1/1,000,000; Ashkenazi and Iraqi Jews 8-9%
- Prolonged aPTT, no effect on PT

Genotype	No. of Subjects†	Factor XI:C	APTT
		% of normal‡	*sec*
II/II	16	1.2±0.5§¶	108±18‖
II/III	23	3.3±1.6	85±22**
III/III	13	9.7±3.8§	67±18
II/–	25	52±18	39±7.4
III/–	22	67±24††	36±7.4‡‡
Controls			
Ashkenazi Jews	58	113±30	ND
Hospital personnel§§	49	103±41	32±4

- Mild bleeding tendency despite FXI<20%, rare spontaneous bleeding
- Exacerbate trauma- or surgery-induced bleeding – GI, urinary tract (urokinase) or nasopharynx (tPA in saliva)

Genotype	Tonsillectomy or Urologic or Nose Surgery	Other Surgical Procedures	Tooth Extraction	Circumcision
	procedures with bleeding/all procedures (no. of patients)			
II/II	5/6 (5)	4/8* (6)	7/11 (11)	0/5
II/III	5/7 (7)	3/20 (8)	11/19 (19)	1/13
III/III	2/3 (3)	1/10 (6)	8/10 (10)	0/4
Total	12/16†	8/38	26/40	1/22

Asakai R, et al. NEJM 1991

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↓ **FXIa** → ↓ **thrombin** → ↓ **TAFI**

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Total	12/16†	8/38	26/40	1/22

Asakai R, et al. NEJM 1991

Association between Factor XI deficiency and the risk of bleeding, cardiovascular, and venous thromboembolic events

Retrospective cohort, nationwide health care databases of Maccabi Healthcare Services in Israel

7403 pts with FXI test:

- 90% normal FXI activity
- 5.0% partial deficiency (15 to <50%)
- 2.9% severe deficiency (<15%)
- 7.9% any deficiency in FXI activity (<50%)

7 matched (age, sex) not tested for FXI (i.e., general population reference group)

Moser SS, et al. Thromb Haemost 2022

	N events	10-year risk (95% CI)	Unadjusted HR (95% CI)	Fully adjusted HR (95% CI)
Severe bleeding				
Severe FXI deficiency (<15%)				
Factor XI cohort, *n* = 209	1	0.50% (0.00–1.50%)	0.54 (0.07–4.15)	0.49 (0.06–3.95)
General population controls, *n* = 1,463	13	1.60% (0.60–2.60%)	Ref.	Ref.
Partial FXI deficiency (15 to <50%)				
Factor XI cohort, *n* = 368	7	2.50% (0.60–4.40%)	5.38 (2.00–14.43)	5.27 (1.91–14.52)
General population controls, *n* = 2,576	9	0.50% (0.20–0.90%)	Ref.	Ref.
Overall FXI deficiency (<50%)				
Factor XI cohort, *n* = 577	8	1.90% (0.50–3.20%)	2.53 (1.13–5.69)	2.56 (1.13–5.81)
General population controls, *n* = 4,039	22	0.90% (0.50–1.30%)	Ref.	Ref.
Clinically relevant nonsevere bleeding				
Severe FXI deficiency (<15%)				
Factor XI cohort, *n* = 213	21	13.80% (7.70–19.60%)	1.55 (0.97–2.49)	1.53 (0.94–2.47)
General population controls, *n* = 1,491	99	10.80% (8.50–13.10%)	Ref.	Ref.
Partial FXI deficiency (15 to <50%)				
Factor XI cohort, *n* = 373	31	10.50% (6.60–14.30%)	1.44 (0.98–2.12)	1.41 (0.95–2.08)
General population controls, *n* = 2,611	151	8.40% (7.00–9.80%)	Ref.	Ref.
Overall FXI deficiency (<50%)				
Factor XI cohort, *n* = 586	52	11.60% (8.30–14.80%)	1.48 (1.10–2.00)	1.45 (1.08–1.97)
General population controls, *n* = 4,102	250	9.20% (8.00–10.40%)	Ref.	Ref.

Overall low risk at 10 years

Most severe bleeding post-procedural:

- After rhinoplasty (n=2)
- Irregular menstrual bleeding with hospitalization (n=1)
- Posthemorrhagic anemia after liver transplant (n=1)
- Rectal bleed after colonoscopy and polypectomy (n=1)
- Lower GI bleed after colonoscopy (on LMWH)(n=1)
- GI bleed (also on VKA) (n=1)
- Subarachnoid hemorrhage (also on antiplatelets)(n=1)

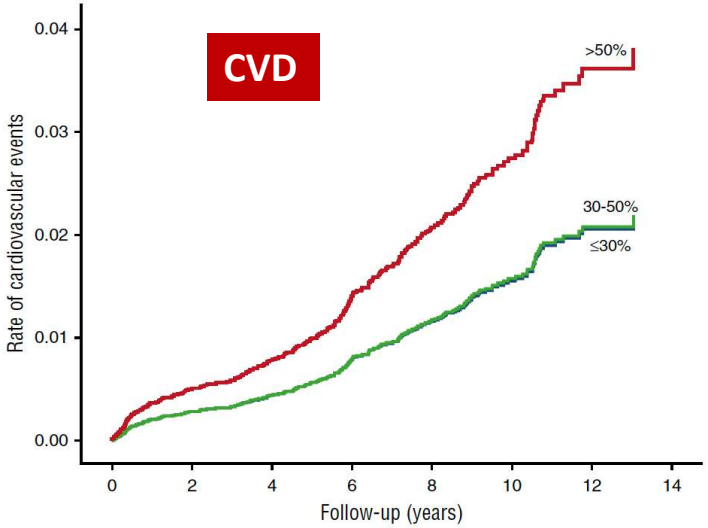
Small numbers
Residual confounding

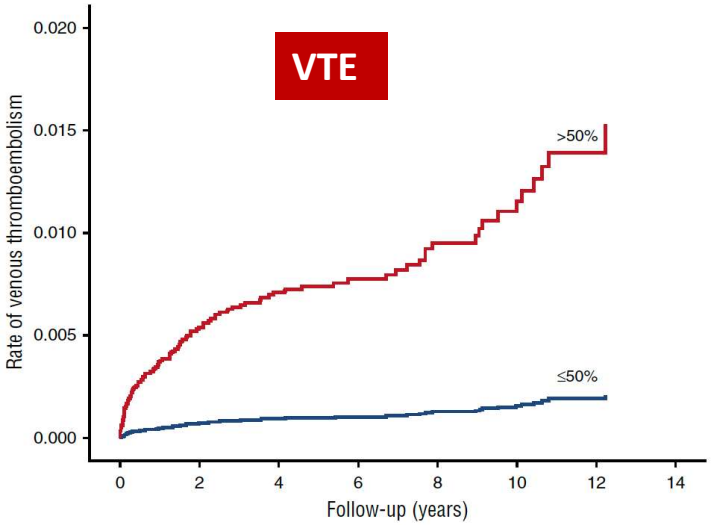
Moser SS, et al. Thromb Haemost 2022

	N events	10-year risk (95% CI)	Unadjusted HR (95% CI)	Fully adjusted HR (95% CI)
CV events				
Severe FXI deficiency (<15%)				
Factor XI cohort, *n* = 208	1	0.50% (0.00–1.60%)	0.48 (0.06–3.63)	0.55 (0.07–4.33)
General population controls, *n* = 1,456	15	1.80% (0.80–2.70%)	Ref.	Ref.
Partial FXI deficiency (15 to <50%)				
Factor XI cohort, *n* = 369	1	0.30% (0.00–0.90%)	0.86 (0.11–6.90)	0.55 (0.06–4.73)
General population controls, *n* = 2,583	8	0.40% (0.10–0.70%)	Ref.	Ref.
Overall FXI deficiency (<50%)				
Factor XI cohort, *n* = 577	2	0.40% (0.00–0.90%)	0.61 (0.14–2.58)	0.55 (0.13–2.36)
General population controls, *n* = 4,039	23	0.90% (0.50–1.20%)	Ref.	Ref.
VTE				
Severe FXI deficiency (<15%)				
Factor XI cohort, *n* = 212	0	0%	N/A	N/A
General population controls, *n* = 1,484	4	0.40% (0.00–0.90%)	N/A	N/A
Partial FXI deficiency (15 to <50%)				
Factor XI cohort, *n* = 371	1	0.30% (0.00–0.90%)	0.76 (0.10–6.04)	0.67 (0.08–5.47)
General population controls, *n* = 2,597	9	0.50% (0.20–0.80%)	Ref.	Ref.
Overall FXI deficiency (<50%)				
Factor XI cohort, *n* = 583	1	0.20% (0.00–0.60%)	0.53 (0.07–4.09)	0.45 (0.06–3.47)
General population controls, *n* = 4,081	13	0.50% (0.20–0.70%)	Ref.	Ref.

Moser SS, et al. Thromb Haemost 2022

Factor XI deficiency is associated with lower risk for CVD and VTE





	Factor XI activity	Number	Events	aHR (95% CI)
Cardiovascular event	≤30%	542	19	0.57 (0.35-0.92)
	30%-50%	693	16	0.51 (0.30-0.87)
	>50%	8958	230	Reference
VTE	≤50%	1235	3	0.26 (0.08-0.84)
	>50%	8958	94	Reference

Preis M, et al. Blood 2017

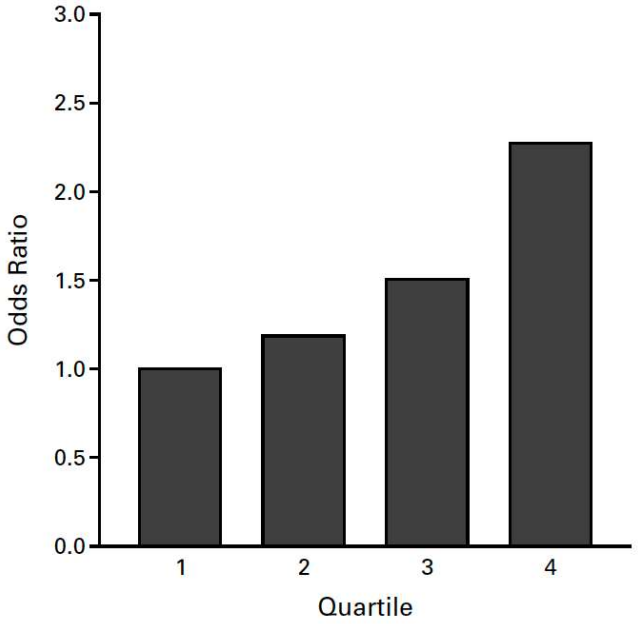
High levels of coagulation factor XI antigen as a risk factor for VTE

Leiden Thrombophilia Study

TABLE 3. RISK OF THROMBOSIS ACCORDING TO FACTOR XI LEVEL.

FACTOR XI*	PATIENTS (N=473)	CONTROLS (N=474)	ODDS RATIO (95% CI)†
≤90th Percentile	381	427	1.0
>90th Percentile	92	47	2.2 (1.5–3.2)
≤95th Percentile	423	451	1.0
>95th Percentile	50	23	2.3 (1.4–3.9)

*The 90th and 95th percentiles of factor XI levels in control subjects were 120.8 and 130.2 percent, respectively, with 100 percent equivalent to the factor XI antigen level in pooled plasma samples from 40 healthy volunteers.



Q1 ≤83.3%; Q2 ≤94.8%; Q3 ≤110.0%; Q4 >110.0 %, with 100 % equivalent to the FXI antigen level in pooled plasma samples from 40 healthy volunteers

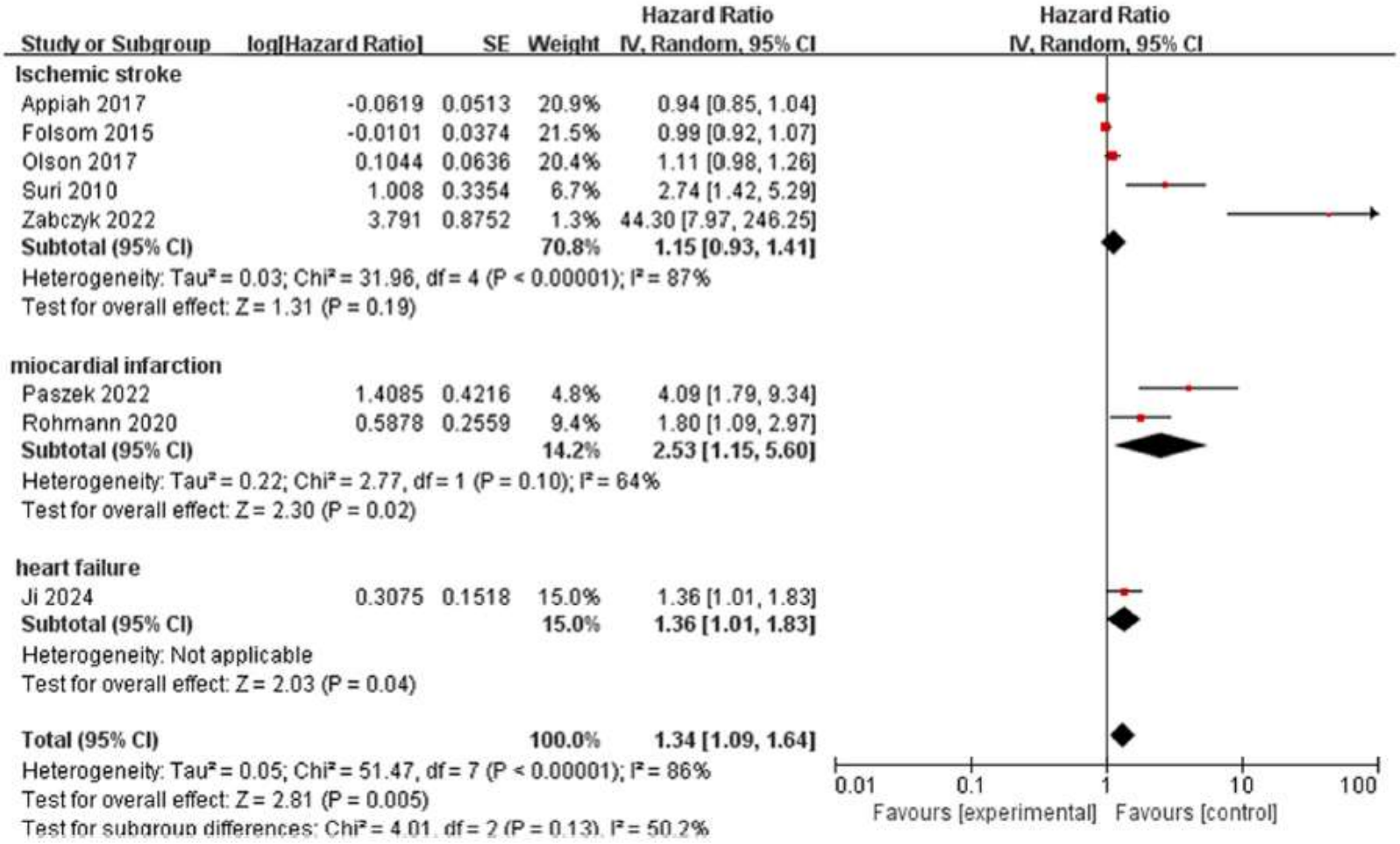
Meijers JCM, et al. NEJM 2000

Associations between fXI and VTE, ischemic stroke, and MI/coronary heart disease

Study	Subjects (*n*)	Variable (assay)	Outcome	Association (yes/no)
Israeli[22]	Inherited fXI deficiency	fXI:c <15%	Protection against DVT	Yes
LITE[20]	Age >45 y (462)	High fXI (fXI:Ag)	VTE	Yes
LETS[23]	Age <70 y (350)	High fXI (fXI:c)	DVT	Yes
Israeli[27]	Inherited fXI deficiency	fXI:c <15%	Protection against IS	Yes
ARIC[26]	Age 45-54 y at intake (15 792)	High fXI (fXII:c)	IS	Yes
Yang[28]	Age <55 y with IS	High fXI (fXI:c)	IS	Yes
RATIO[25]	Females age 18-50 y with IS (175)	High fXI (fXIa-C1-INH; fXIa-AT INH)	IS	Yes
RATIO[34]	Females age 18-50 y with IS (175)	High fXI (fXI:Ag)	IS	Yes
Israeli[32]	Inherited fXI deficiency	fXI:c <15%	Protection against MI	No
ARIC[33]	Age 45-54 y at intake (15 792)	High fXI (fXI:c)	CHD	No
SMILE[30]	Males age <70 y with MI (560)	High fXI (fXI:c)	MI	Yes
NPHS-II[24]	Males age 50-63 y at intake (2997)	High fXI (fXIa-C1-INH; fXIa-AT INH)	CHD	No
RATIO[25]	Females age 18-50, with MI (205)	High fXI (fXIa-C1-INH; fXIa-AT INH)	MI	No
RATIO[31]	Females age 18-50, with MI (205)	High fXI (fXI:c)	MI	No
RATIO[34]	Females age 18-50, with MI (205)	High fXI (fXI:Ag)	MI	No

Key N. Hematology 2014

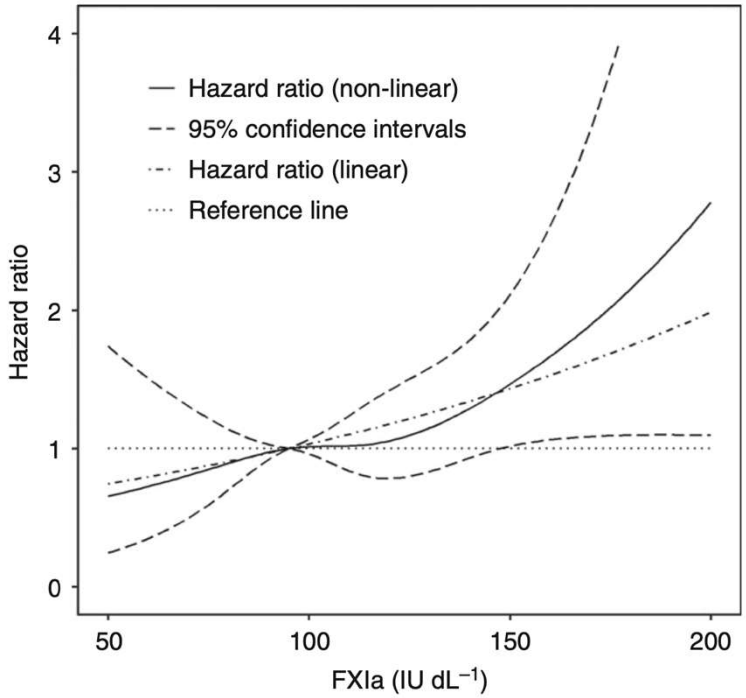
Factor XI levels and the risk of cardiovascular events: a systematic review and meta-analysis of case-control and cohort studies



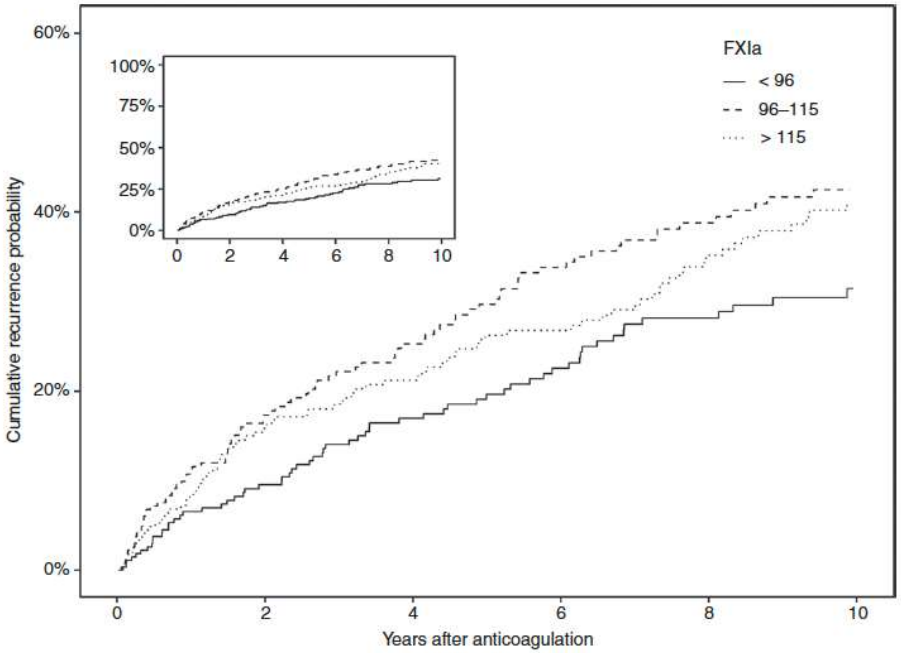
Li W, et al. RPTH 2025

Factor XI and recurrent VTE

FXIa in 851 patients with unprovoked VTE in whom anticoagulation had been stopped



aHR 0.94 for each decrease of 10 IU/dL in FXIa



Recurrent VTE by FXIa tertiles

Kyrle PA, J Thromb Haemost 2019

No association between FXII activity or antigen and risk of VTE

Leiden Thrombophilia study (LETS)

Table I. Thrombosis risk for strata of factor XII.

Factor XII activity (%)	Patients	Controls	Odds ratio (95% CI)
⩾100	198	190	1*
60–100	129	138	0·9 (0·7–1·2)
30–60	21	20	1·0 (0·5–2·0)
<30	2	2	1·0 (0·1–7·0)

* Reference category.

LITE study

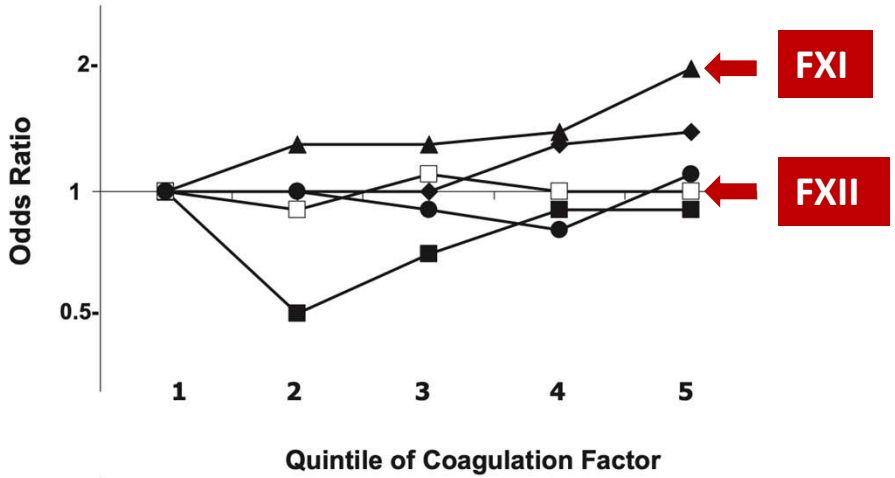


Figure 1. Odds ratios of venous thromboembolism by quintiles of coagulation factors. Analyses were adjusted for age, sex, race, and study. ♦ represents factor IX; ■, factor X; ▲, factor XI; □, factor XII; and ●, factor XIII. Fifth quintile cutoffs are 167% for factor IX, 161% for factor X, 157% for factor XI, 179% for factor XII, and 171% for factor XIII.

Only high FXI associated with risk of future VTE

Koster T, Br J Haematol 1994
Cushman M, Blood 2009

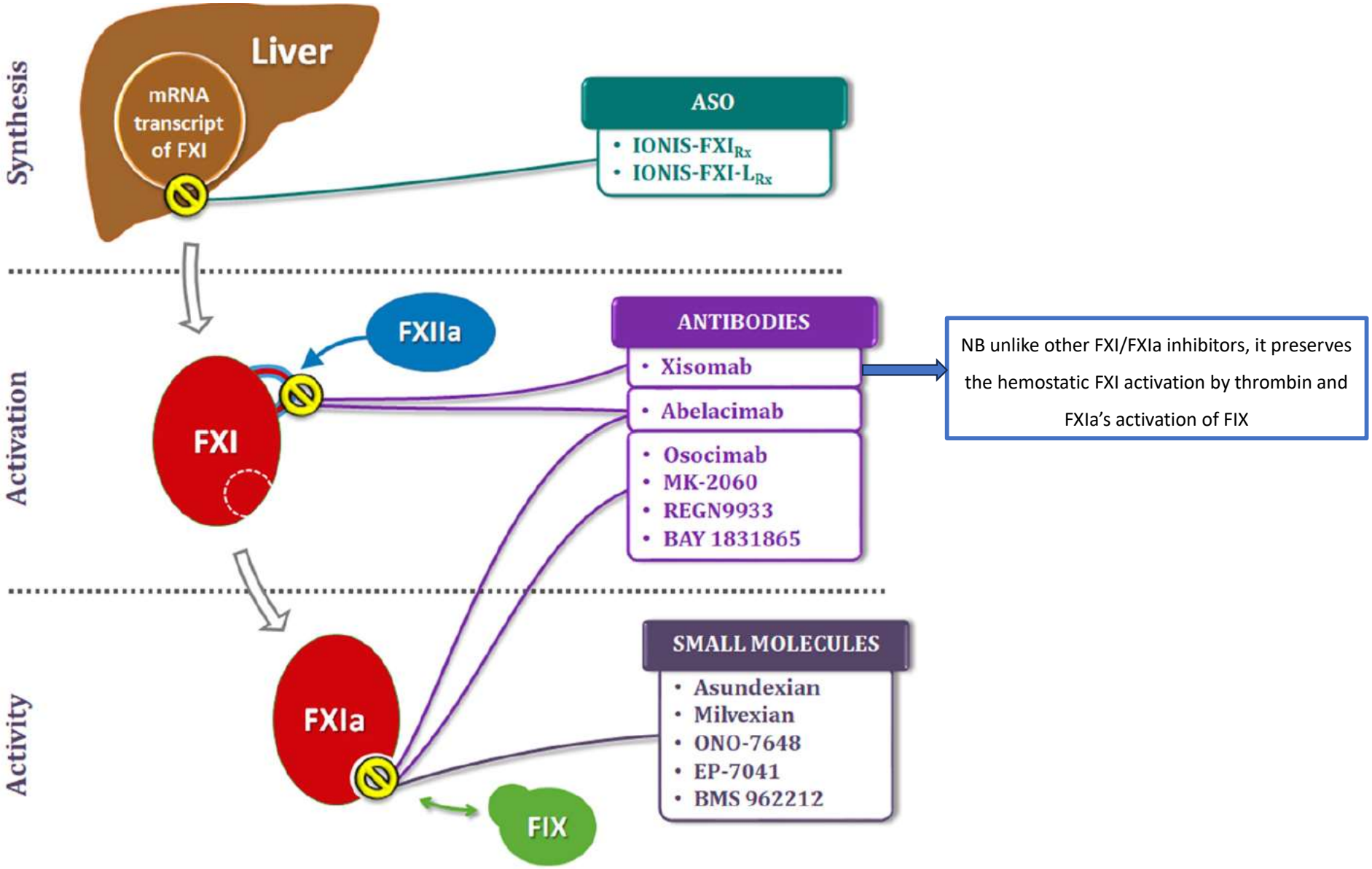
Associations between fXII and VTE, ischemic stroke, and MI/coronary heart disease

Study	Subjects (*n*)	Variable (assay)	Outcome	Association (yes/no)	Comment
Viennese[15]	51% male (8936)	Low fXII (fXII:c)	All-cause mortality	Yes	"U"-Shaped curve
LETS[19]	Age <70 y (350)	Low fXII (fXII:c)	DVT	No	
LITE[20]	Age >45 y (462)	Low fXII (fXII:Ag)	VTE	No	VTE also not associated with high fXII
NPHS-II[24]	Males age 50-63 y at intake (2997)	Low fXII (fXIIa-C1-INH)	IS	Yes	
RATIO[25]	Females age 18-50 y with IS (175)	High fXII (fXIIa-C1-INH)	IS	Yes	Risk further increased by OCPs
RATIO[34]	Females age 18-50 y with IS (175)	High fXII (fXII:Ag)	IS	No	fXII:Ag not correlated with fXIIa-C1-INH
ARIC[26]	Age 45-54 y at intake (15 792)	High fXII (fXII:c)	IS	No	Case-control within ARIC cohort
NPHS-II[29]	Males age 50-63 y at intake (2997)	High fXII (fXIIa:Ag)	CHD	Yes	
NPHS-II[24]	Males age 50-63 y at intake (2997)	High fXII (fXIIa-C1-INH)	CHD	No	
RATIO[25]	Females age 18-50 y with MI (205)	High fXII (fXIIa-C1-INH)	MI	No	Low fXII-CI INH also not associated with MI
RATIO[34]	Females age 18-50 y with MI (205)	High fXII (fXII:Ag)	MI	No	fXII:Ag not correlated with fXIIa-C1 INH
SMILE[30]	Males age <70 y with MI (560)	Low fXII (fXII:c)	MI	Yes	Increased risk with high fXI:c
ARIC[33]	Age 45-54 y at intake (15 792)	High fXII (fXII:c)	CHD	No	Case-control within ARIC cohort

Key N. Hematology 2014

Outline

- Limitations of current anticoagulant treatments
- Role of FXI in hemostasis, thrombosis, and CAT
- Preclinical and epidemiological evidence supporting FXI as a safer target than FXa
- Clinical studies with FXI inhibitors
- Reversal agents and interference with coagulation assays
- Conclusions and future directions

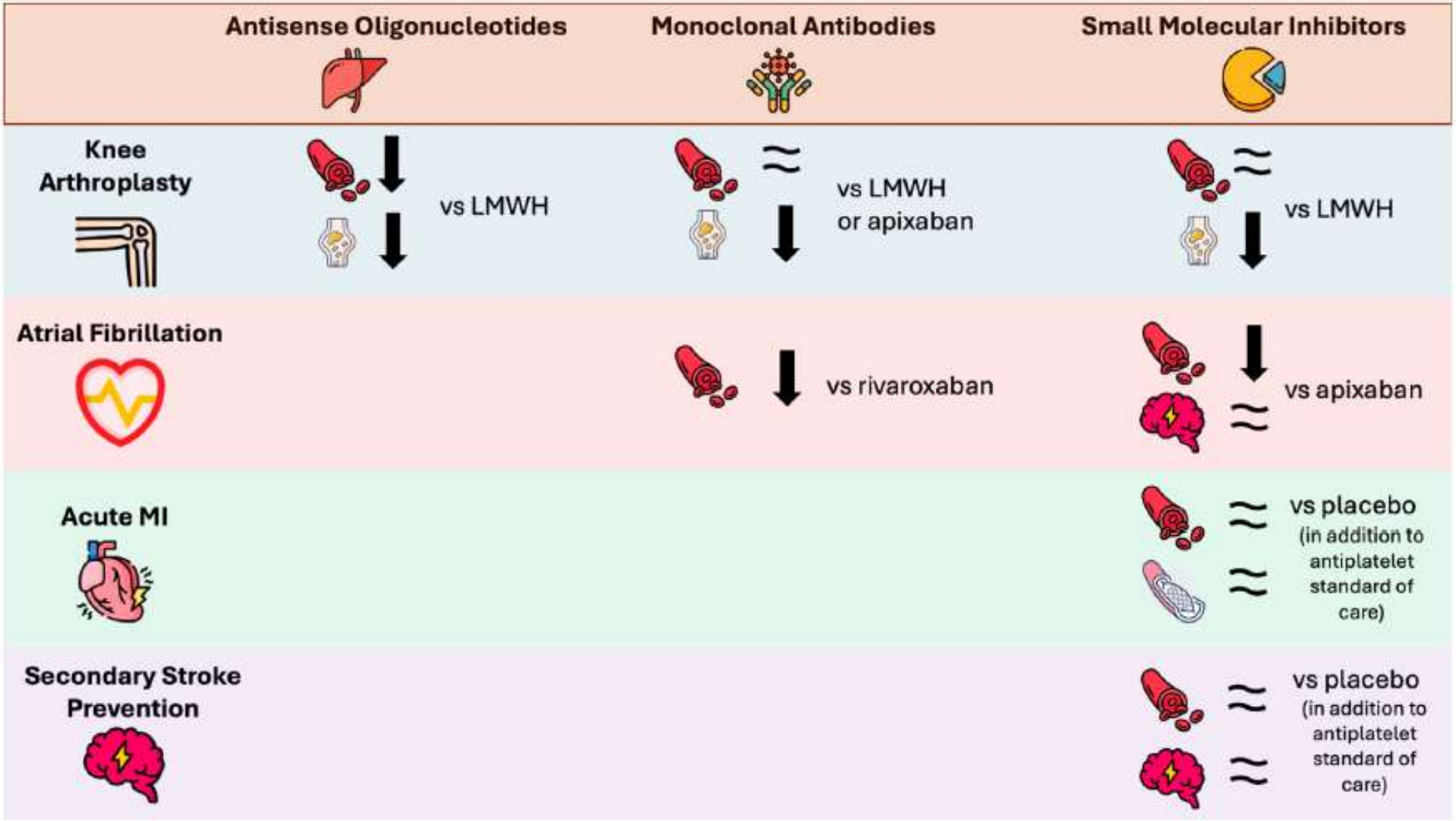


Badimon JJ, et al. J Cardioivasc Develop Dis 2022

	Antisense oligonucleotides (fesomersen)	Monoclonal antibodies (abelacimab, gruticibart, osocimab)	Small molecules (asundexian, milvexian)
Mechanism of action	Block synthesis	Bind target protein	Bind target protein
Administration route	Subcutaneous	Intravenous or subcutaneous	Oral
Administration frequency	Weekly to monthly	Monthly	Daily
Onset of action	Slow (weeks)	Rapid (hours to days)	Rapid (1 to 4 hours)
Offset of action	Slow (weeks)	Slow (weeks)	Rapid (12 to 24 hours)
Renal clearance	No	No	Yes*
CYP450 metabolism	No	No	Yes
Potential for DDIs	No	No	Yes

*Asundenxian < 15%, milvexian <20%

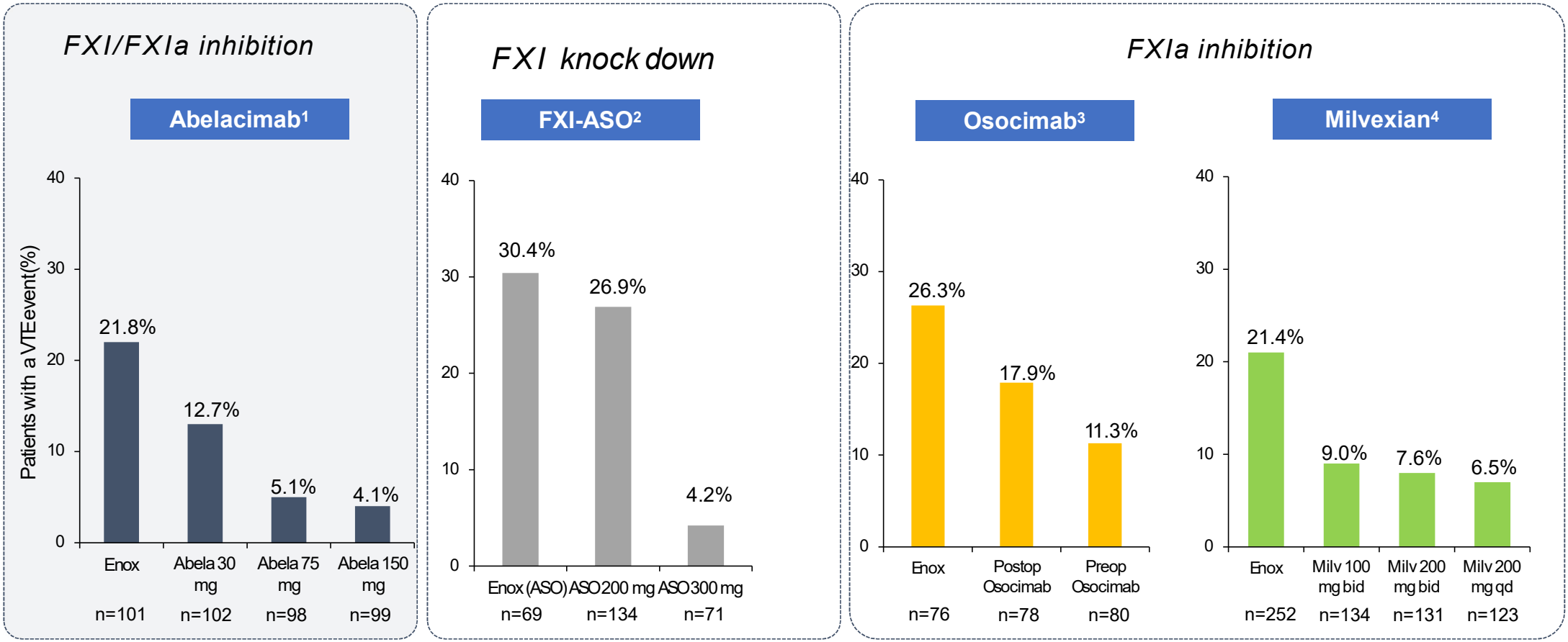
Modified from Di Nisio M, et al. BTVB 2024



Barnes GD. JTH 2025

Demonstration of antithrombotic 'proof-of-concept'

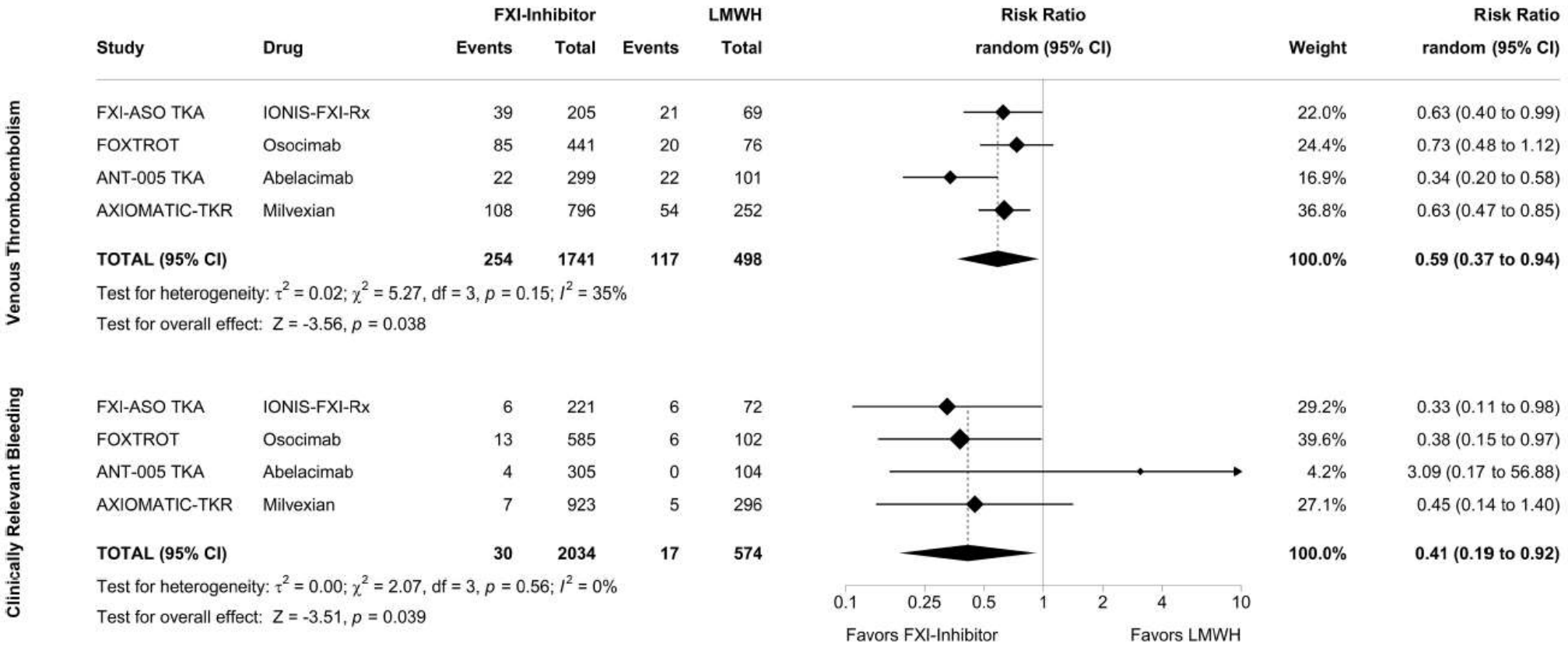
Cross-study comparison of FXI agents in TKA



ASO: antisense olignonucleotide; Enox: enoxaparin

[1]Verhamme et al. NEJM (2021) [2] Buller et al. NEJM (2015); [3] Weitz et al. JAMA (2020); [4]Weitz et al. NEJM (2021)

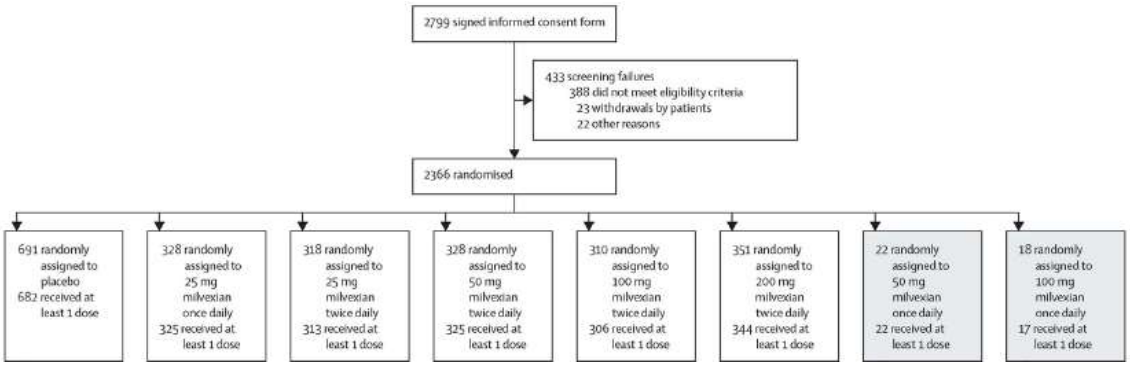
Factor XI inhibitors for VTE prevention



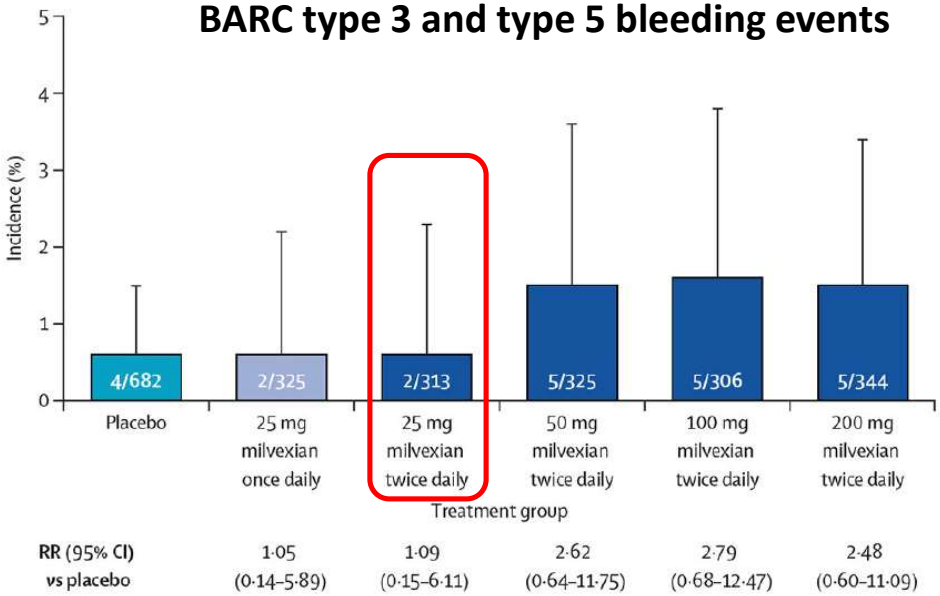
Nopp S, et al. Frontiers Cardiovasc Med 2022

Milvexian for secondary stroke prevention (AXIOMATIC-SSP): a phase 2, international, randomised, double-blind, placebo-controlled, dose-finding trial

2366 pts with ischemic stroke/high-risk TIA



BARC type 3 and type 5 bleeding events



Milvexian, added to dual antiplatelet therapy, did not reduce the composite of symptomatic ischaemic stroke or covert brain infarction and did not increase major bleeding

Sharma M, et al. Lancet Neurol 2024

	Placebo (n=625)	25 mg milvexian once daily (n=308)	25 mg milvexian twice daily (n=287)	50 mg milvexian twice daily (n=306)	100 mg milvexian twice daily (n=277)	200 mg milvexian twice daily (n=317)
Participants with composite event*	104 (17%)	50 (16%)	53 (18%)	43 (14%)	41 (15%)	52 (16%)
Symptomatic ischaemic stroke	38 (6%)	15 (5%)	12 (4%)	13 (4%)	11 (4%)	27 (9%)
Covert infarcts	66 (11%)	35 (11%)	41 (14%)	30 (10%)	30 (11%)	25 (8%)
Model-based estimate for composite event (90·2% CI)†	16·8% (14·5 to 19·1)	16·7% (14·8 to 18·6)	16·6% (14·8 to 18·3)	15·6% (13·9 to 17·5)	15·4% (13·4 to 17·6)	15·3% (12·8 to 19·7)
RR (90·2% CI), model-based analysis†	..	0·99 (0·91 to 1·05)	0·99 (0·87 to 1·11)	0·93 (0·78 to 1·11)	0·92 (0·75 to 1·13)	0·91 (0·72 to 1·26)
Risk difference (90·2% CI) versus placebo, model-based analysis‡	..	–0·1 (–1·7 to 0·8)	–0·2 (–2·4 to 1·6)	–1·2 (–4·0 to 1·7)	–1·4 (–4·6 to 2·0)	–1·5 (–5·1 to 3·9)

But fewer symptomatic strokes

Sharma M, et al. Lancet Neurol 2024

The PACIFIC Phase II program with over 4000 pts

PACIFIC AF

Atrial fibrillation

20 mg asundexian
50 mg asundexian
Apixaban

755 patients
Results presented at ACC 2022 and published in *Lancet* 2022[1]

PACIFIC AMI

Acute myocardial infarction

10 mg asundexian
20 mg asundexian
50 mg asundexian
Placebo

+ DAPT

1601 patients
Results presented at ESC 2022 and published in *Circulation* 2022[2]

PACIFIC STROKE

Non-cardioembolic ischemic stroke

10 mg asundexian
20 mg asundexian
50 mg asundexian
Placebo

+ SAPT or DAPT

1808 patients
Results presented at ESC 2022 and published in *Lancet* 2022[3]

Asundexian is currently undergoing clinical trials and has not yet been approved in Europe.

ACC, American College of Cardiology; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; SAPT, single antiplatelet therapy.

1. Piccini JP *et al. Lancet* 2022;399:1383–1390. 2. Rao SV *et al. Circulation* 2022;146:1196–1206. 3. Shoamanesh A *et al. Lancet* 2022;400:997–1007.

PACIFIC AMI

1601 patients with AMI, on dual antiplatelet (80% ASA + ticagrelor or prasugrel), 99% PCI

Oral asundexian 10, 20, or 50 mg or placebo once daily for 6 to 12 months

	Asundexian 10 mg N=395	Asundexian 20 mg N=397	Asundexian 50 mg N=402	Placebo N=399
BARC bleeding 2,3,5	30 (7.59)	32 (8.06)	42 (10.45)	36 (9.02)
Cardiovascular death, MI, stroke, or stent thrombosis	27 (6.80)	24 (5.99)	22 (5.47)	22 (5.49)

No increase in bleeding and low rate of ischemic events

Rao SV, et al. Circulation 2022

PACIFIC-Stroke

Randomised, double-blind, placebo-controlled, phase 2b

1808 pts with acute (<48 h) non-cardioembolic ischaemic stroke treated with antiplatelets (43% dual). MRI at 26 weeks

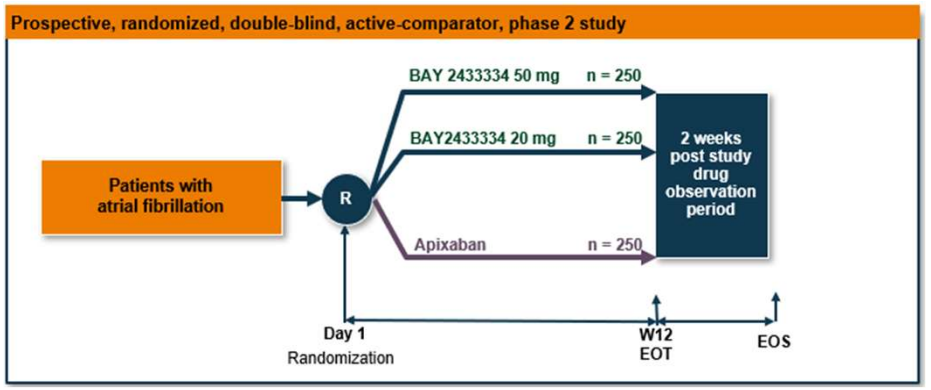
	Placebo (n=456)	Asundexian 10 mg (n=455)	Asundexian 10 mg *vs* placebo	Asundexian 20 mg (n=450)	Asundexian 20 mg *vs* placebo	Asundexian 50 mg (n=447)	Asundexian 50 mg *vs* placebo
Ischaemic stroke or covert infarcts	87 (19%)	86 (19%)	0·99 (0·79–1·24)	99 (22%)	1·15 (0·93–1·43)	90 (20%)	1·06 (0·85–1·32)
Recurrent symptomatic ischaemic stroke or TIA	38 (8%)	35 (8%)	0·92 (0·63–1·35)	28 (6%)	0·74 (0·49–1·12)	24 (5%)	0·64 (0·41–0·98)
ISTH-defined major and CRNM bleeding	11 (2%)	19 (4%)	1·71 (0·91–3·18)	14 (3%)	1·27 (0·66–2·47)	19 (4%)	1·74 (0·93–3·24)

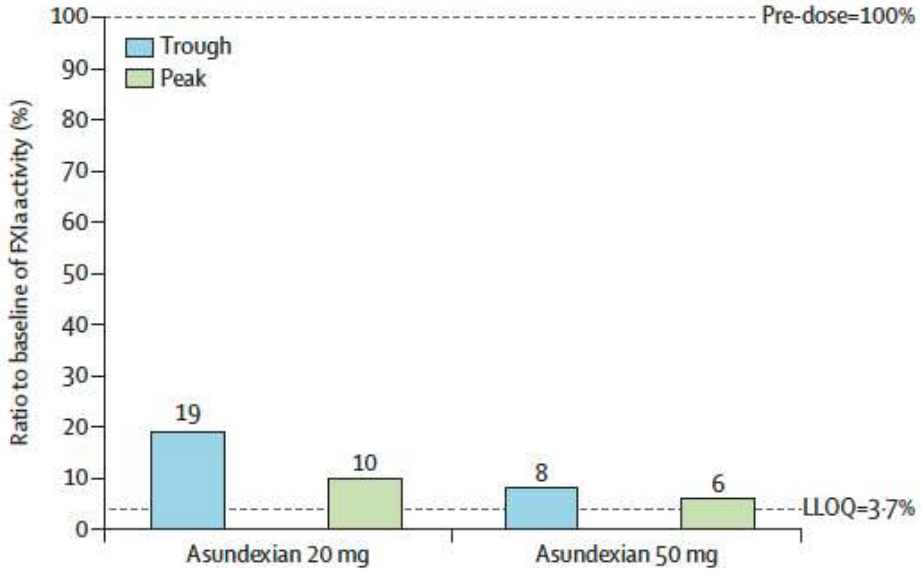
No reduction of incident covert brain infarction or ischaemic stroke. No increase of clinically relevant bleeding

Shoamanesh A, et al. Lancet 2022

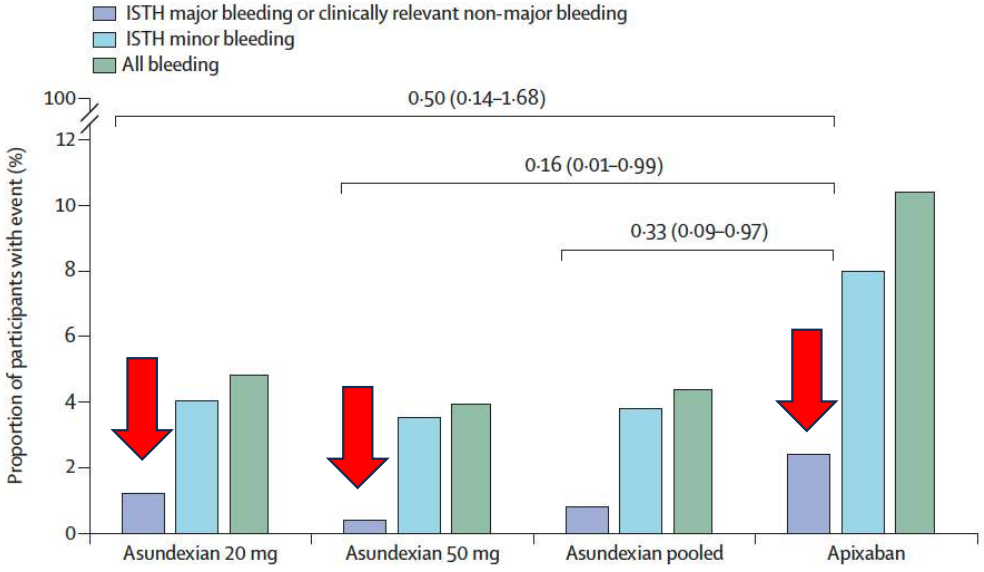
Asundexian vs apixaban in AF (PACIFIC-AF)

755 AF pts ≥45 years, CHA2DS2-VASc ≥2 (male) or ≥3 (female)





After 4 weeks



No major bleeding

Piccini JP, et al. Lancet 2022

Exploratory thrombotic endpoints

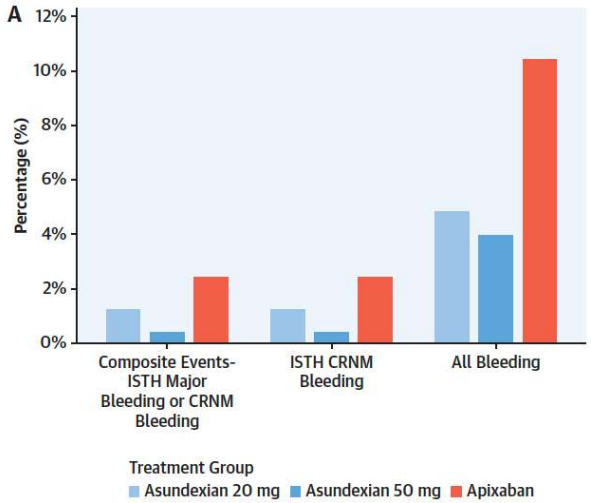
	Asundexian 20 mg N=251	Asundexian 50 mg N=254	Apixaban N=250
Cardiovascular death	1	3	3
Myocardial infarction	0	1	0
Ischemic stroke	2	1	0
Systemic embolism	0	0	0

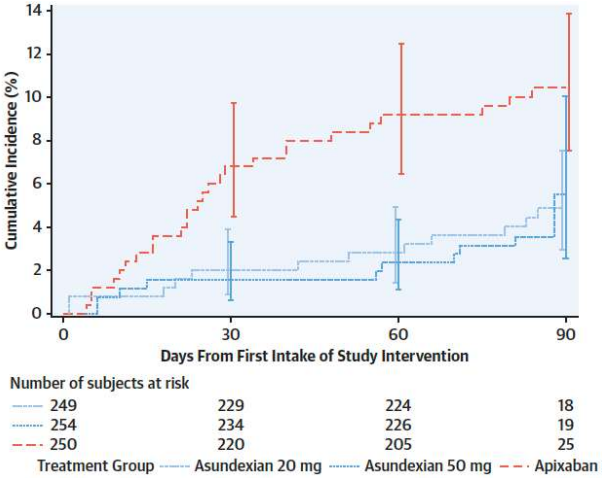
Piccini JP, et al. Lancet 2022

Bleeding Outcomes in Patients Treated With Asundexian in Phase II Trials

Vs Apixaban

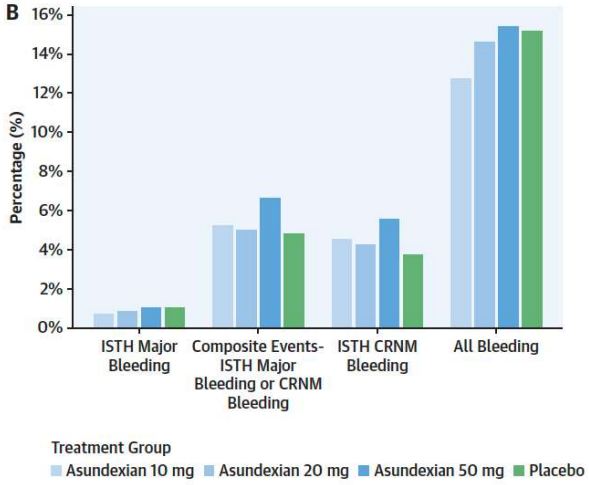
Asundexian 20 mg and 50 mg od: less bleeding, early reduction within the first 30 days

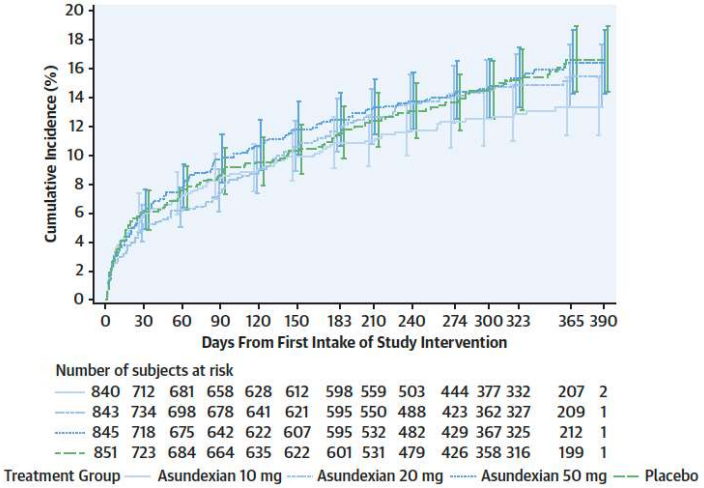




Vs placebo

Asundexian 10 mg, 20 mg, and 50 mg od: similar rates of major and all bleeding asundexian 50 mg higher rate of CRNMB

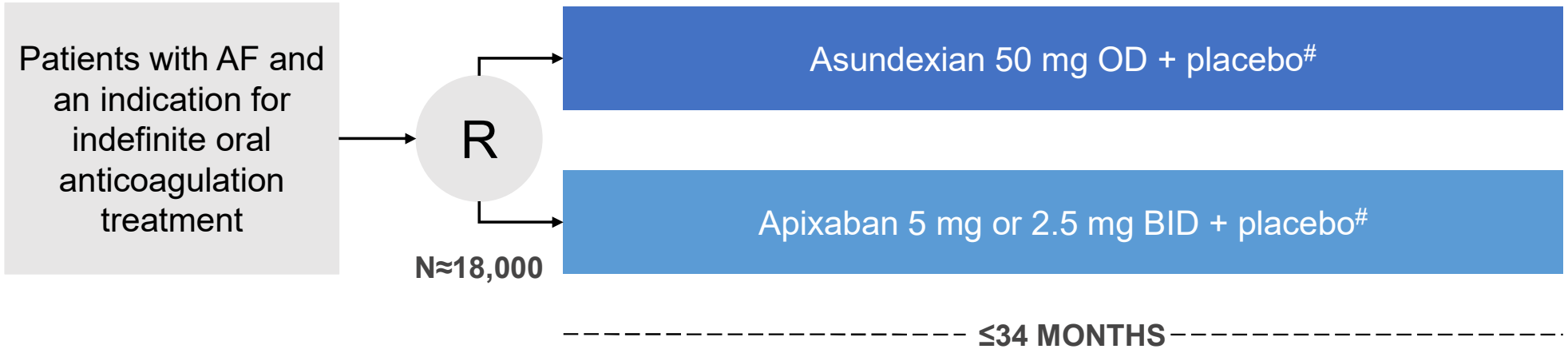




Eikelboom JW, et al. JACC 2024

Phase III OCEANIC-AF Study Design[1,2]

Multicenter, international, randomized, double-blind, double-dummy, parallel group and 2-arm Phase III study of the oral FXIa inhibitor asundexian compared with apixaban for the prevention of stroke or systemic embolism in medium/high-risk patients with AF (active, recruiting)*



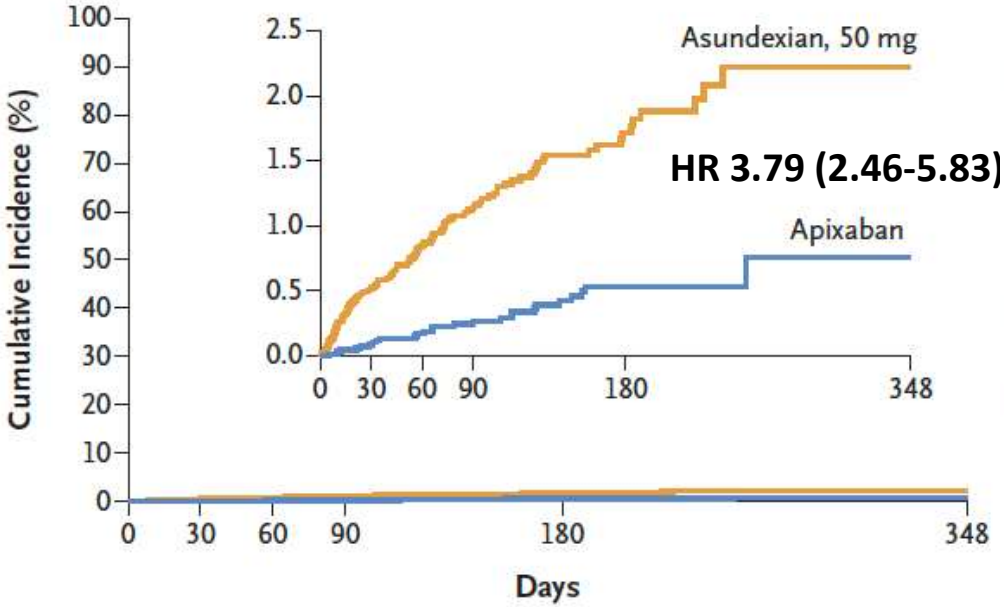
Primary efficacy outcome: Time to first occurrence of composite of stroke or systemic embolism
Primary safety outcome: Time to first occurrence of ISTH major bleeding

*OCEANIC-AF is a Phase III study following the Phase II study PACIFIC-AF. #Placebo required to account for BID dosing of apixaban compared with OD dosing of Asundexian.

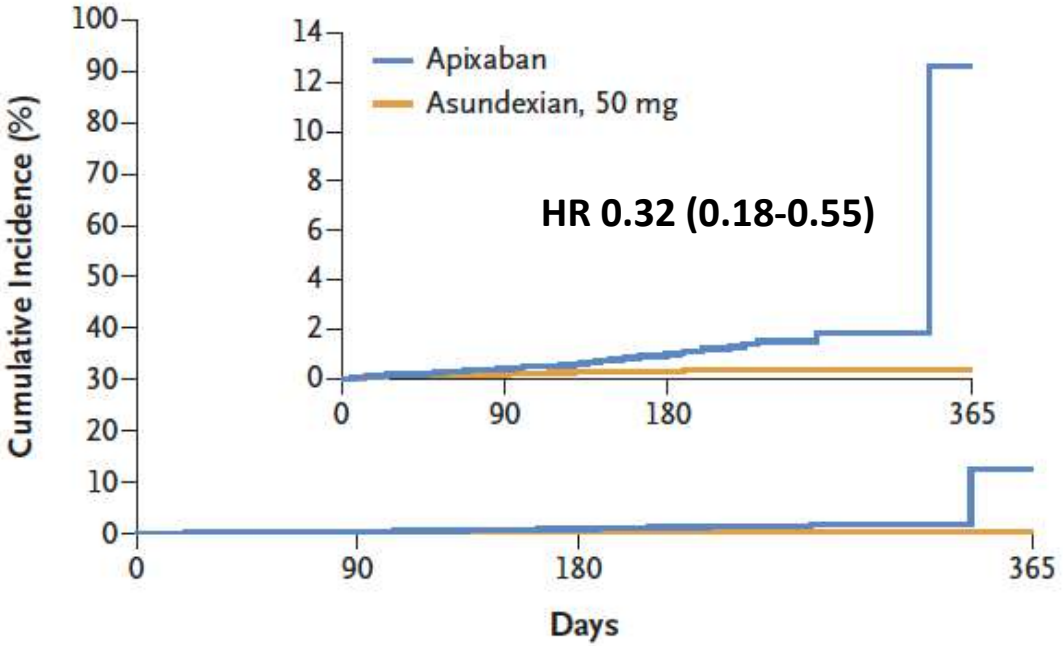
AF, arial fibrillation; BID, twice daily; ISTH, International Society on Thrombosis and Haemostasis; OD, once daily; R, randomization.

1. Bayer. 2023. https://clinicaltrials.gov/ct2/show/NCT05643573. 2. Bayer AG. https://www.bayer.com/media/en-us/bayer-initiates-landmark-phase-iii-study-program-to-investigate-oral-fxia-inhibitor-asundexian/ [both accessed 9 March 2023].

Stroke or Systemic Embolism



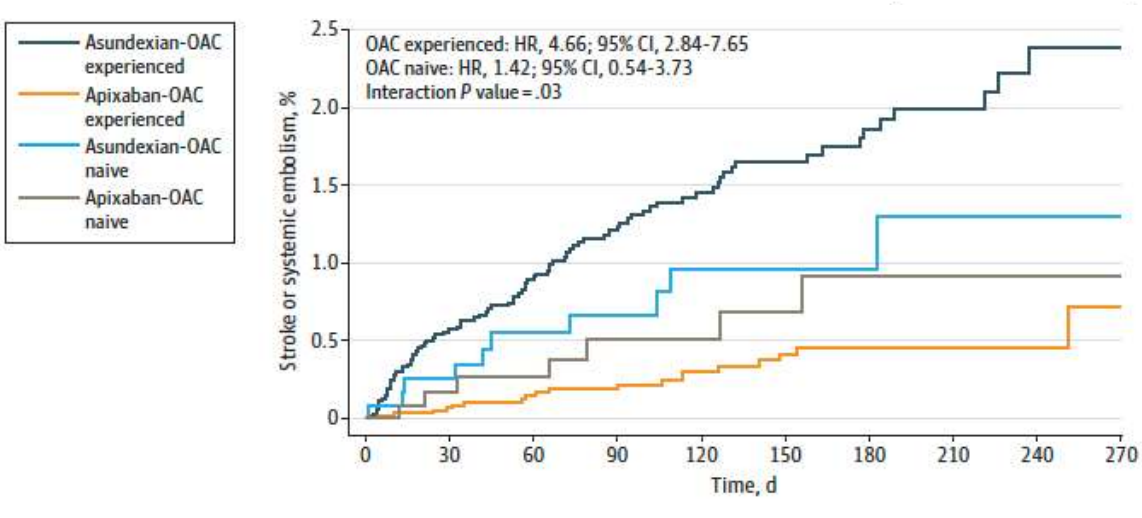
Major Bleeding



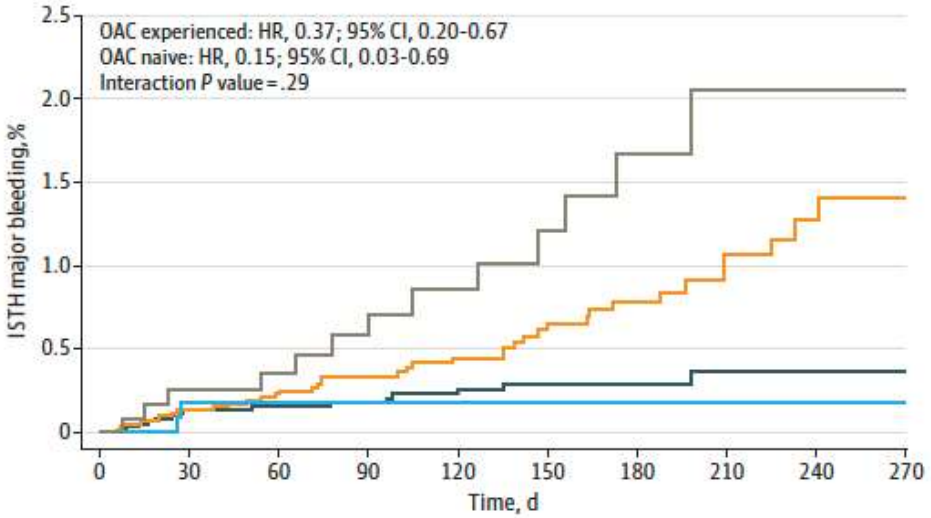
- Intracranial bleeding <0.1% vs 0.2%; HR 0.16 (0.05-0.55)
- Fatal bleeding 0 vs 0.1%

Piccini JP. NEJM 2024

Stroke or Systemic Embolism



Major Bleeding



AF pts OAC naive had a smaller increase in stroke/systemic embolism and similar lower rate of bleeding with asundexian compared with apixaban than patients who were OAC experienced

OAC naive ≤ 6 wks prior use
OAC experienced > 6 wks prior OAC use

Alexander JH, et al. JAMA Cardiol 2025

Stroke or systemic embolism with asundexian: similar in OAC naive, higher in OAC experienced

	OAC naive (n = 2493)					OAC experienced (n = 12 317)					
	Asundexian (n = 1238)		Apixaban (n = 1255)			Asundexian (n = 6177)		Apixaban (n = 6140)			
Outcome	No. (%)	Events/100 patient-years (95% CI)	No. (%)	Events/100 patient-years (95% CI)	HR (95% CI)	No. (%)	Events/100 patient-years (95% CI)	No. (%)	Events/100 patient-years (95% CI)	HR (95% CI)	*P* value for interaction
Primary efficacy outcome (stroke or systemic embolism)	10/1238 (0.8)	2.45 (1.18-4.19)	7/1255 (0.6)	1.73 (0.70-3.23)	1.42 (0.54-3.73)	88/6177 (1.4)	4.12 (3.31-5.03)	19/6140 (0.3)	0.88 (0.53-1.32)	4.66 (2.84-7.65)	.03
Ischemic stroke or systemic embolism	10/1238 (0.8)	2.45 (1.18-4.19)	5/1255 (0.4)	1.24 (0.40-2.53)	2.00 (0.68-5.85)	86/6177 (1.4)	4.03 (3.22-4.92)	17/6140 (0.3)	0.79 (0.46-1.21)	5.09 (3.02-8.56)	.12
Ischemic stroke	9/1238 (0.7)	2.21 (1.01-3.86)	5/1255 (0.4)	1.24 (0.40-2.53)	1.80 (0.60-5.39)	76/6177 (1.2)	3.55 (2.80-4.40)	16/6140 (0.3)	0.74 (0.43-1.15)	4.77 (2.78-8.18)	.12
CV death	8/1238 (0.6)	1.95 (0.84-3.52)	11/1255 (0.9)	2.71 (1.35-4.53)	0.77 (0.31-1.92)	40/6177 (0.6)	1.86 (1.33-2.47)	33/6140 (0.5)	1.53 (1.05-2.10)	1.21 (0.76-1.92)	.33
CV death, MI, or stroke	25/1238 (2.0)	6.17 (3.99-8.81)	20/1255 (1.6)	4.95 (3.02-7.34)	1.31 (0.72-2.35)	130/6177 (2.1)	6.10 (5.09-7.19)	57/6140 (0.9)	2.65 (2.01-3.38)	2.29 (1.68-3.13)	.08
All-cause death	9/1238 (0.7)	2.19 (1.00-3.84)	17/1255 (1.4)	4.19 (2.44-6.40)	0.56 (0.25-1.26)	51/6177 (0.8)	2.37 (1.76-3.06)	54/6140 (0.9)	2.51 (1.88-3.22)	0.94 (0.64-1.38)	.22

OAC naive ≤ 6 wks prior use
OAC experienced > 6 wks prior OAC use

Alexander JH, et al. JAMA Cardiol 2025

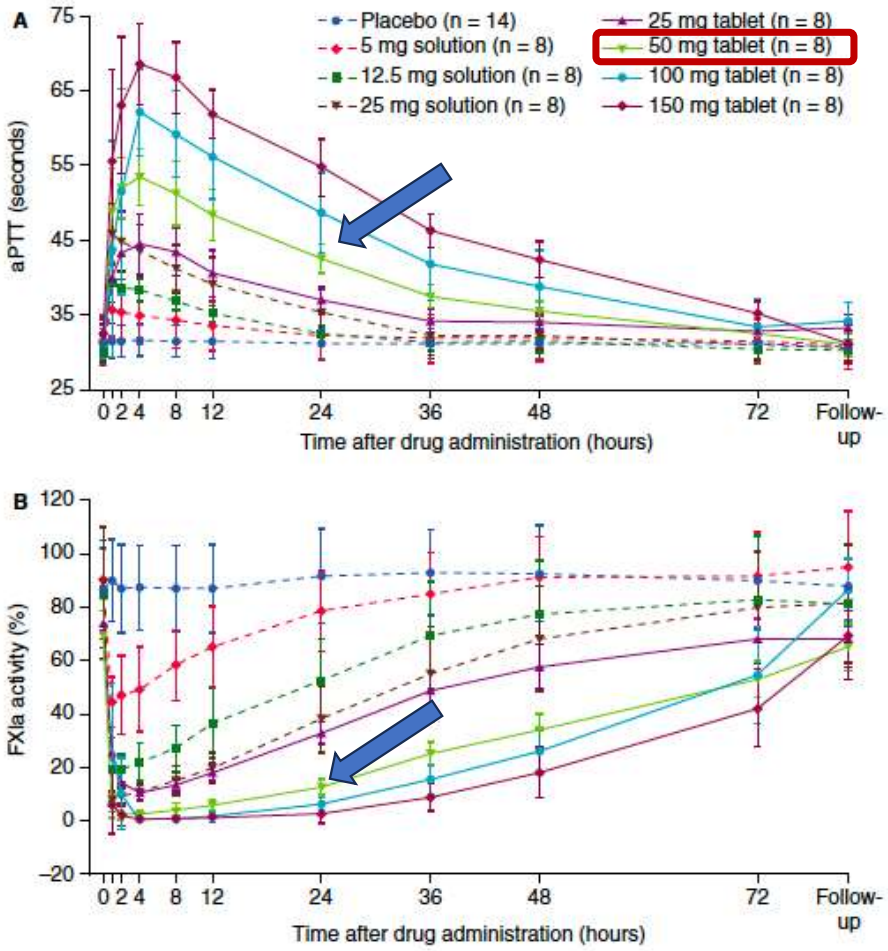
Bleeding with asundexian: lower in both OAC naive and OAC experienced

	OAC naive (N = 2477)					OAC experienced (N = 12 260)					
	Asundexian (n = 1228)		Apixaban (n = 1249)			Asundexian (n = 6145)		Apixaban (n = 6115)			
Outcome	No. (%)	Events/100 patient-years (95% CI)	No. (%)	Events/100 patient-years (95% CI)	HR (95% CI)	No. (%)	Events/100 patient-years (95% CI)	No. (%)	Events/100 patient-years (95% CI)	HR (95% CI)	*P* value for interaction
ISTH major bleeding	2/1228 (0.2)	0.46 (0.06-1.28)	13/1249 (1.0)	2.98 (1.59-4.80)	0.15 (0.03-0.69)	15/6145 (0.2)	0.66 (0.37-1.03)	40/6115 (0.7)	1.73 (1.24-2.31)	0.37 (0.20-0.67)	.29
ISTH major or CRNM bleeding	12/1228 (1.0)	2.77 (1.43-4.54)	41/1249 (3.3)	9.52 (6.83-12.64)	0.29 (0.15-0.56)	71/6145 (1.2)	3.12 (2.44-3.89)	147/6115 (2.4)	6.43 (5.43-7.51)	0.48 (0.36-0.64)	.17
Hemorrhagic stroke	0/1228 (0)	NA	2/1249 (0.2)	0.46 (0.06-1.27)	NA	1/6145 (<0.1)	0.04 (0-0.16)	4/6115 (0.1)	0.17 (0.05-0.38)	0.25 (0.03-2.28)	>.99
Fatal bleeding	0/1228 (0)	NA	1/1249 (0.1)	0.23 (0.01-0.84)	NA	0/6145 (0)	NA	3/6115 (<0.1)	0.13 (0.03-0.31)	NA	NA
Any (ISTH major, CRNM, or minor) bleeding	37/1228 (3.0)	8.66 (6.10-11.67)	90/1249 (7.2)	21.55 (17.33-26.22)	0.40 (0.28-0.59)	226/6145 (3.7)	10.12 (8.85-11.48)	400/6115 (6.5)	18.07 (16.34-19.88)	0.56 (0.47-0.66)	.14

OAC naive ≤ 6 wks prior use
OAC experienced > 6 wks prior OAC use

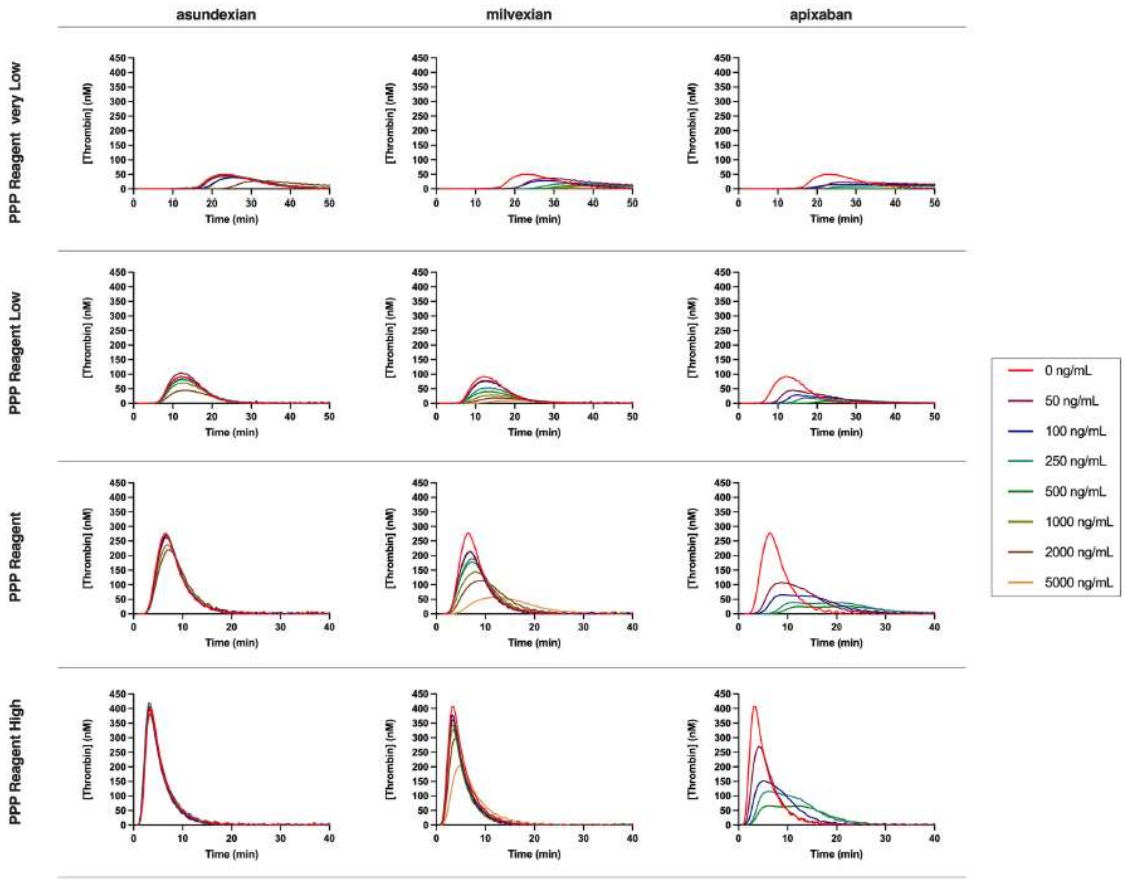
Alexander JH, et al. JAMA Cardiol 2025

Effects of increasing doses of BAY 2433334 on (A) APTT and (B) FXIa activity in healthy volunteers



Thomas D, et al. JTH 2021

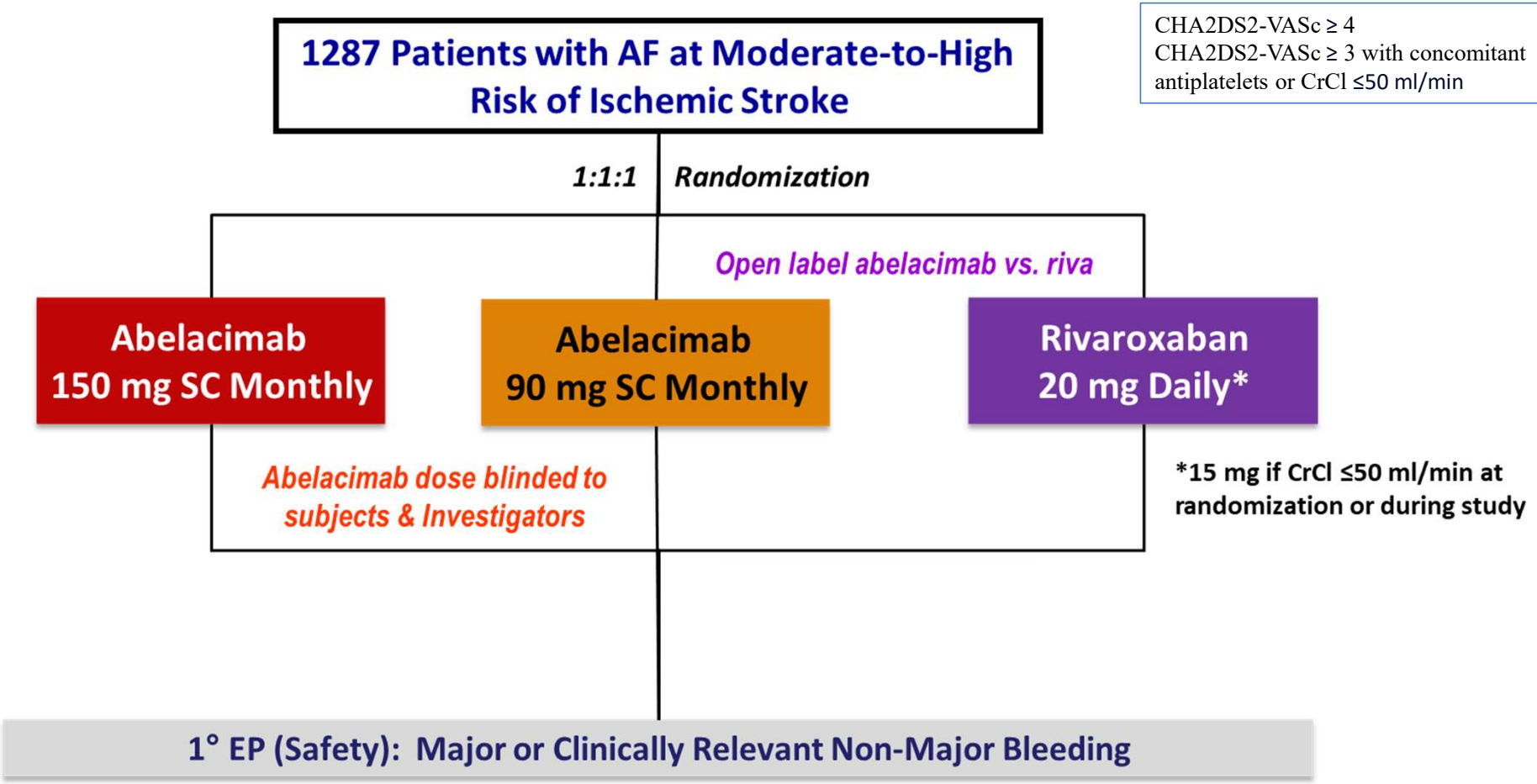
Asundexian in atrial fibrillation: Can pharmacodynamic data explain the failure?



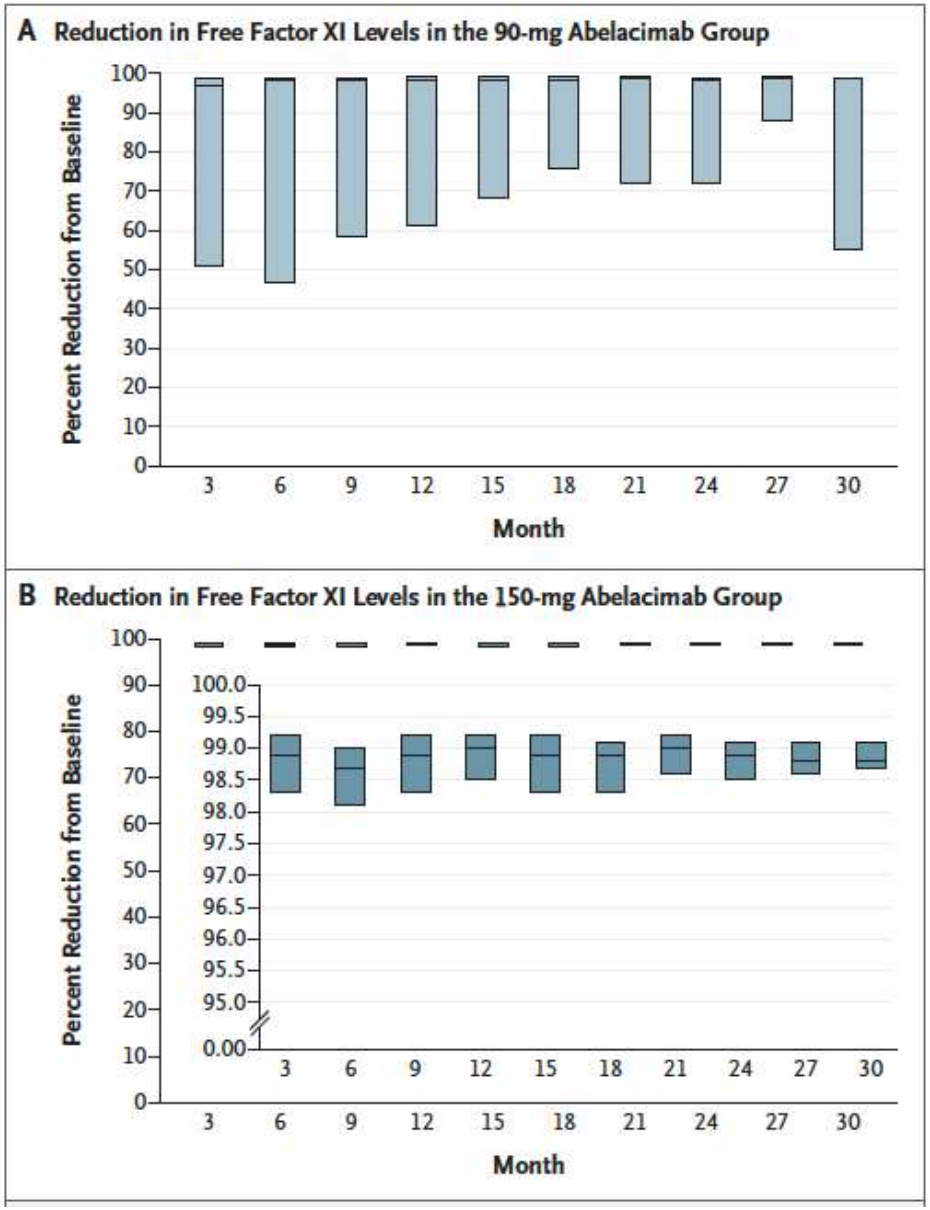
Even if asundexian exhibits longer half-life than milvexian (i.e., ≅ 20 h versus ≅ 10 h), its capacity to inhibit thrombin generation sufficiently during the entire dose interval is lower and probably insufficient for AF patients

Vassart J, et al. Th Res 2024

AZALEA-TIMI 71 Trial Design, Phase IIb



Ruff CTet al. *AHA Scientific Sessions* 2023, Late-breaking Clinical Trial



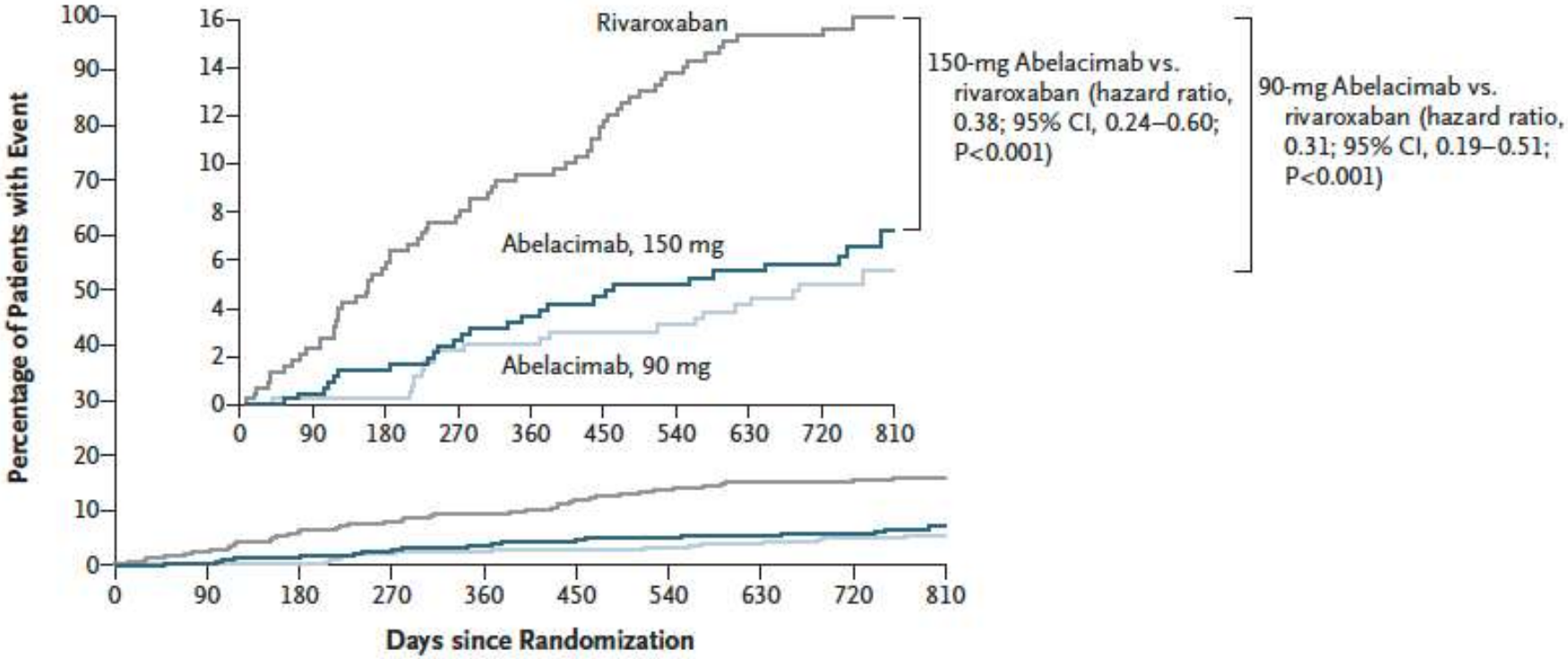
At 3 months

90-mg group 97% (IQR, **51 to 99**)

150-mg group 99% (IQR, 98 to 99)

Ruff CT, et al. NEJM 2025

Major or Clinically Relevant Nonmajor Bleeding



Ruff CT, et al. NEJM 2025

End Point	Rivaroxaban (N=428)		Abelacimab, 150 mg (N=427)			Abelacimab, 90 mg (N=425)		
	Patients with Event	Incidence Rate	Patients with Event	Incidence Rate	Hazard Ratio vs. Rivaroxaban (95% CI)	Patients with Event	Incidence Rate	Hazard Ratio vs. Rivaroxaban (95% CI)
	no. (%)	*events/100 person-yr*	*no. (%)*	*events/100 person-yr*		*no. (%)*	*events/100 person-yr*	
Primary end point: major or clinically relevant nonmajor bleeding	66 (15.4)	8.38	26 (6.1)	3.22	0.38 (0.24–0.60)†	21 (4.9)	2.64	0.31 (0.19–0.51)†
Secondary end points								
Major bleeding	31 (7.2)	3.73	10 (2.3)	1.22	0.33 (0.16–0.66)	8 (1.9)	0.99	0.26 (0.12–0.57)
Gastrointestinal bleeding	18 (4.2)	2.14	2 (0.5)	0.24	0.11 (0.03–0.48)	2 (0.5)	0.25	0.11 (0.03–0.49)
Intracranial hemorrhage	4 (0.9)	0.47	2 (0.5)	0.24	0.51 (0.09–2.78)	4 (0.9)	0.49	1.05 (0.26–4.19)
Other major bleeding	9 (2.1)	1.06	6 (1.4)	0.73	0.68 (0.24–1.91)	2 (0.5)	0.25	0.23 (0.05–1.06)
Major, clinically relevant nonmajor, or minor bleeding	112 (26.2)	15.30	78 (18.3)	10.43	0.68 (0.51–0.91)	53 (12.5)	7.04	0.46 (0.33–0.64)
Exploratory end points								
Stroke or systemic embolism	7 (1.6)	0.83	10 (2.3)	1.21	1.47 (0.56–3.85)	11 (2.6)	1.36	1.65 (0.64–4.25)
Ischemic stroke	5 (1.2)	0.59	10 (2.3)	1.21	2.06 (0.70–6.02)	10 (2.4)	1.24	2.10 (0.72–6.14)
Hemorrhagic stroke	2 (0.5)	0.23	0	0	0	1 (0.2)	0.12	0.52 (0.05–5.72)
Systemic embolism	0	0	1 (0.2)	0.12	NA	0	0	NA
Death from any cause	30 (7.0)	3.52	22 (5.2)	2.65	0.77 (0.44–1.34)	26 (6.1)	3.20	0.93 (0.55–1.58)
Net clinical outcome‡	92 (21.5)	11.75	52 (12.2)	6.45	0.55 (0.39–0.77)	54 (12.7)	6.82	0.58 (0.41–0.81)
Death or any stroke	36 (8.4)	4.25	31 (7.3)	3.75	0.90 (0.56–1.46)	36 (8.5)	4.45	1.07 (0.67–1.70)

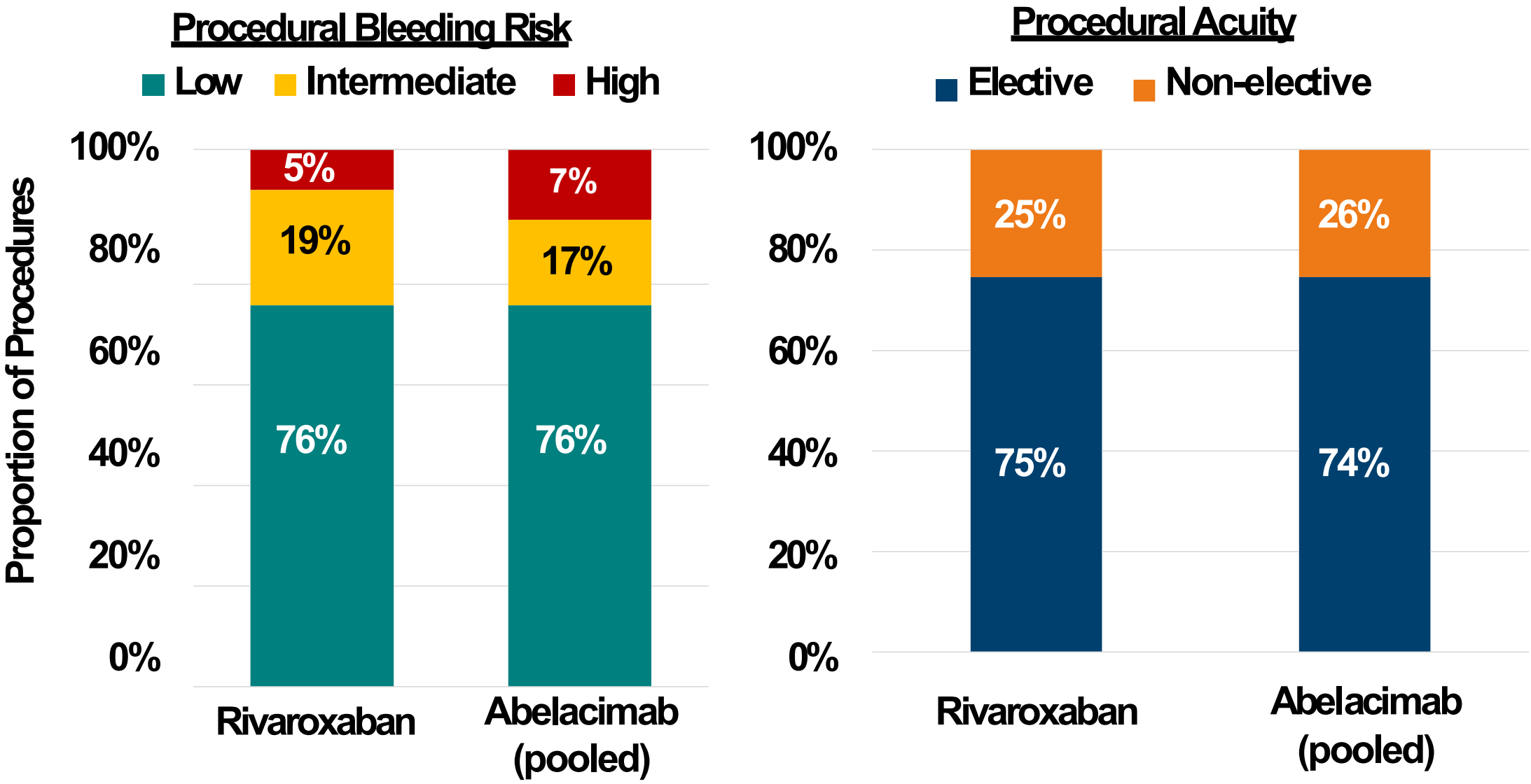
Ruff CT, et al. NEJM 2025

AZALEA Peri-procedural Guidance

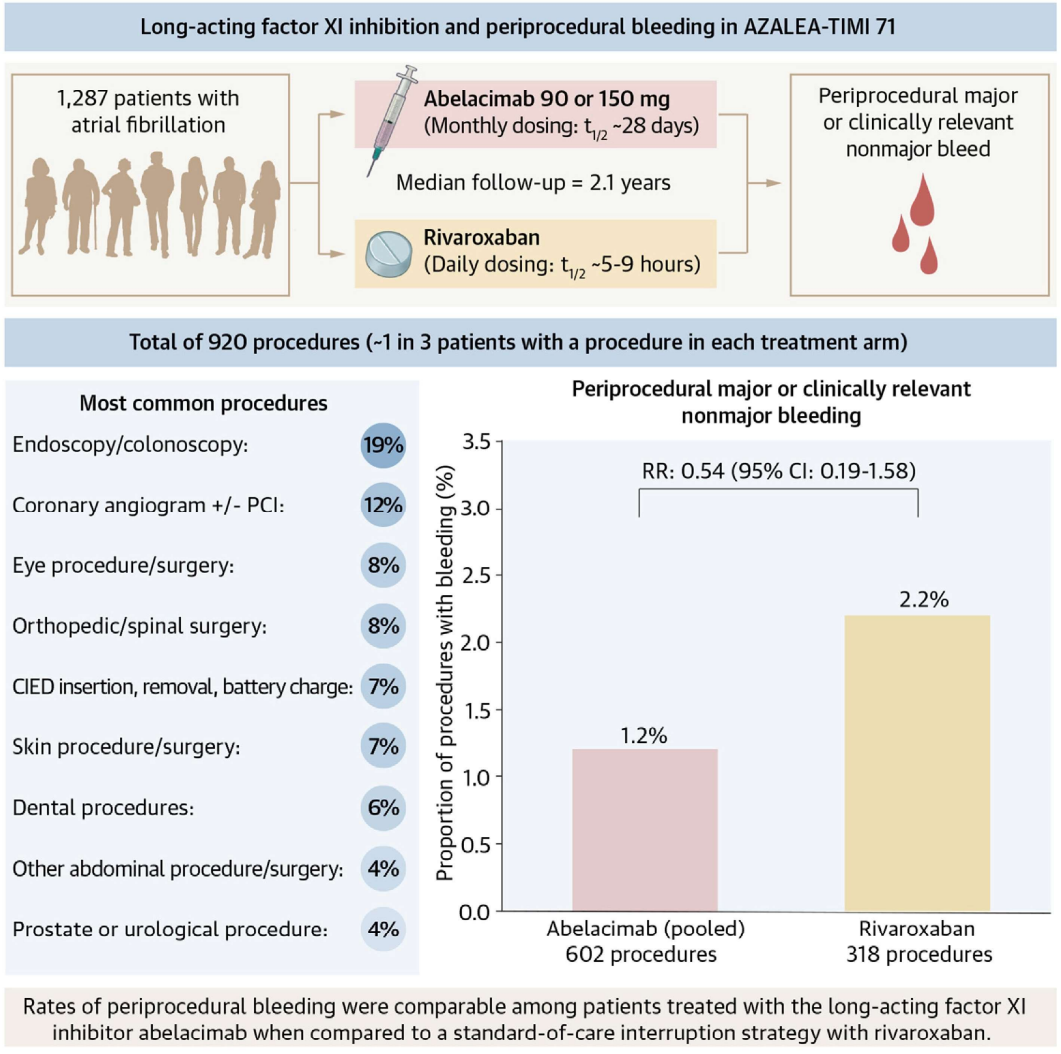
Bleeding Risk	Low Risk	Intermediate-High Risk	Very High Risk	
Procedure example	Coronary angiography	Colonoscopy w/ polypectomy	Spinal surgery, open thoracic or abdominal surgery	
Abelacimab guidance	No interruption or therapy	No interruption; consider anti-fibrinolytic (e.g., TXA) pre-procedurally	**Elective** Interrupt abelacimab	**Non-elective** Consider anti-fibrinolytic + low-dose rVIIa
Rivaroxaban guidance	Interruption per SoC (~24-48h prior to procedure based on CrCl)			

Application of guidance & perceived procedural bleeding risk based on local site's judgement

Procedural Bleeding Risk and Acuity



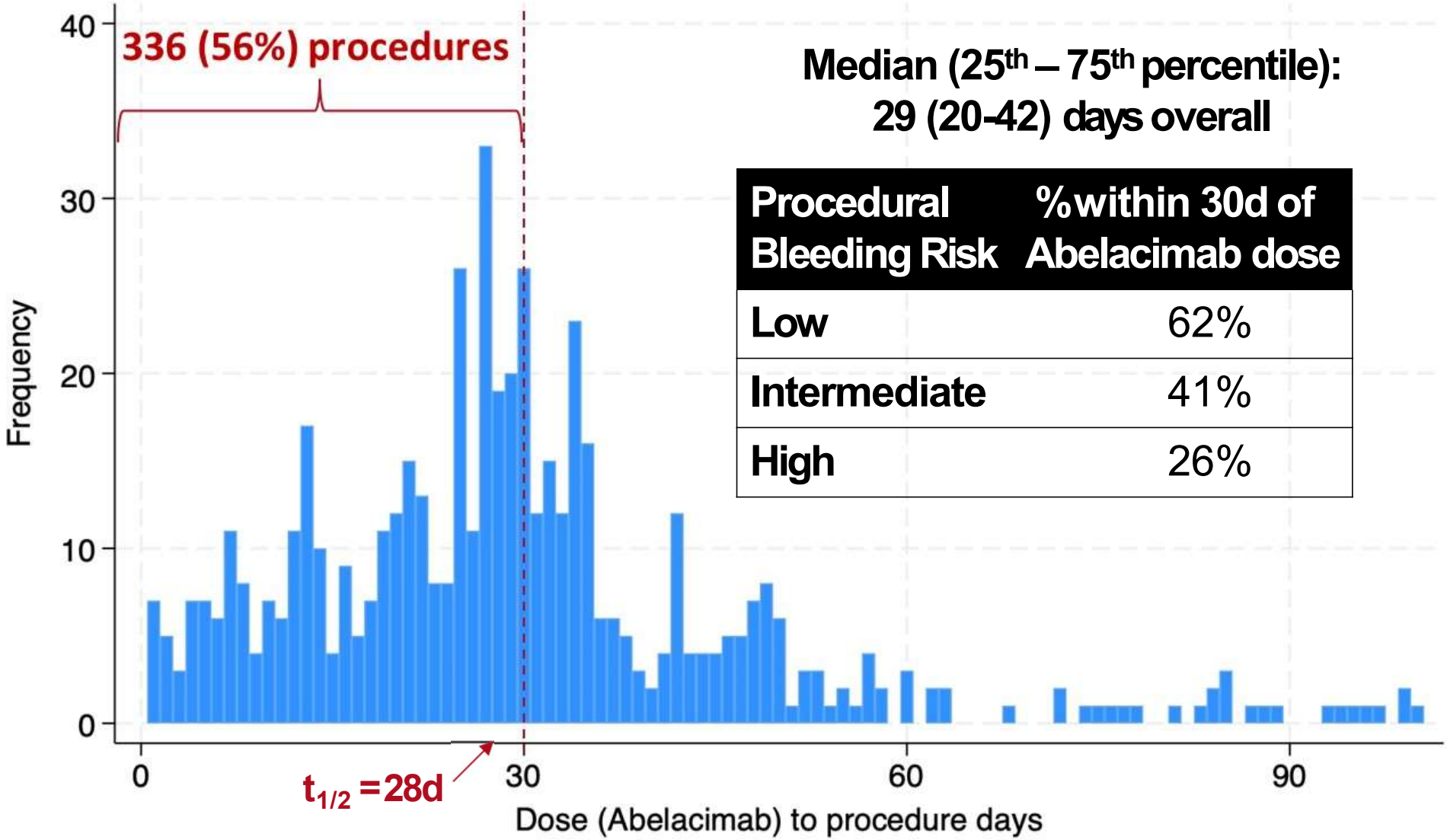
CENTRAL ILLUSTRATION: Long-Acting Factor XI Inhibition and Periprocedural Bleeding



Rates of periprocedural bleeding were comparable among patients treated with the long-acting factor XI inhibitor abelacimab when compared to a standard-of-care interruption strategy with rivaroxaban.

Patel SM, et al. JACC. 2025;85(23):2288-2298.

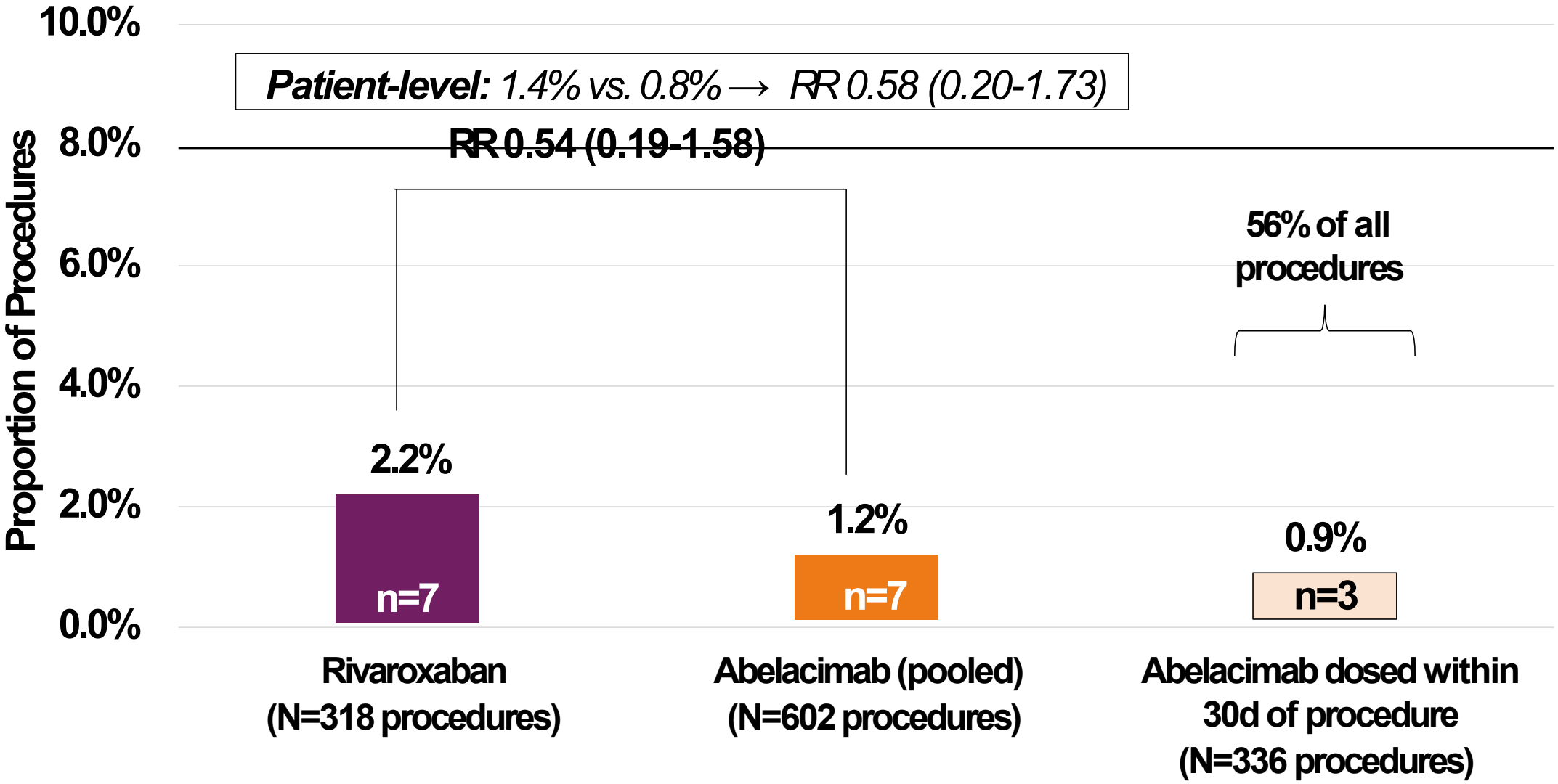
Time from Last Abelacimab Dose to Procedure



Median (25th – 75th percentile):
29 (20-42) days overall

Procedural Bleeding Risk	%within 30d of Abelacimab dose
Low	62%
Intermediate	41%
High	26%

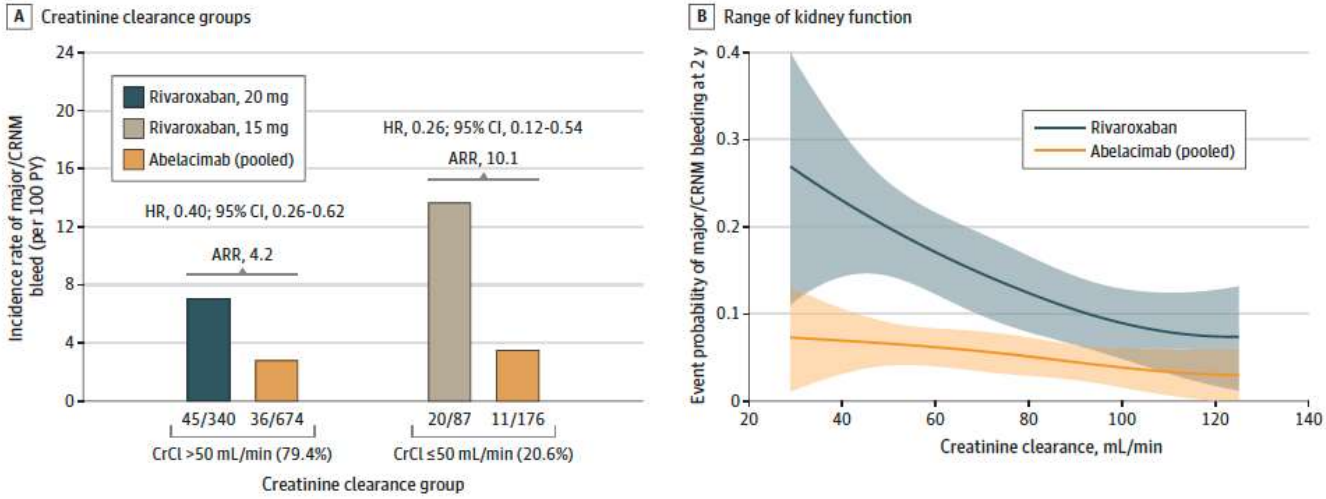
Major or CRNM Bleeding(Procedure-level)



Hemostatic Therapies and Transfusions

Hemostatic Therapy	Proportion of Procedures	
	Rivaroxaban (N=318)	Abelacimab (N=602)
Hemostatic Therapies	**2.5%**	**6.6%**
Anti-fibrinolytic (e.g., tranexamic acid)	0.9%	5.1%
Topical hemostatic agent	0%	0.8%
Fresh frozen plasma	0.9%	0.2%
Recombinant factor VIIa	0%	0%
Other	0.6%	0.5%
Represents therapies used both pre-/intra-procedurally (>95%) or for bleeding		
Blood Transfusions	**5.3%**	**1.2%**

Prespecified analysis of the AZALEA-TIMI 71: by kidney function



CrCl > 50 mL/min rivaroxaban 20mg daily,
CrCl ≤ 50 mL/min rivaroxaban 15mg daily
CrCl ≤ 15 mL/min or dialysis excluded

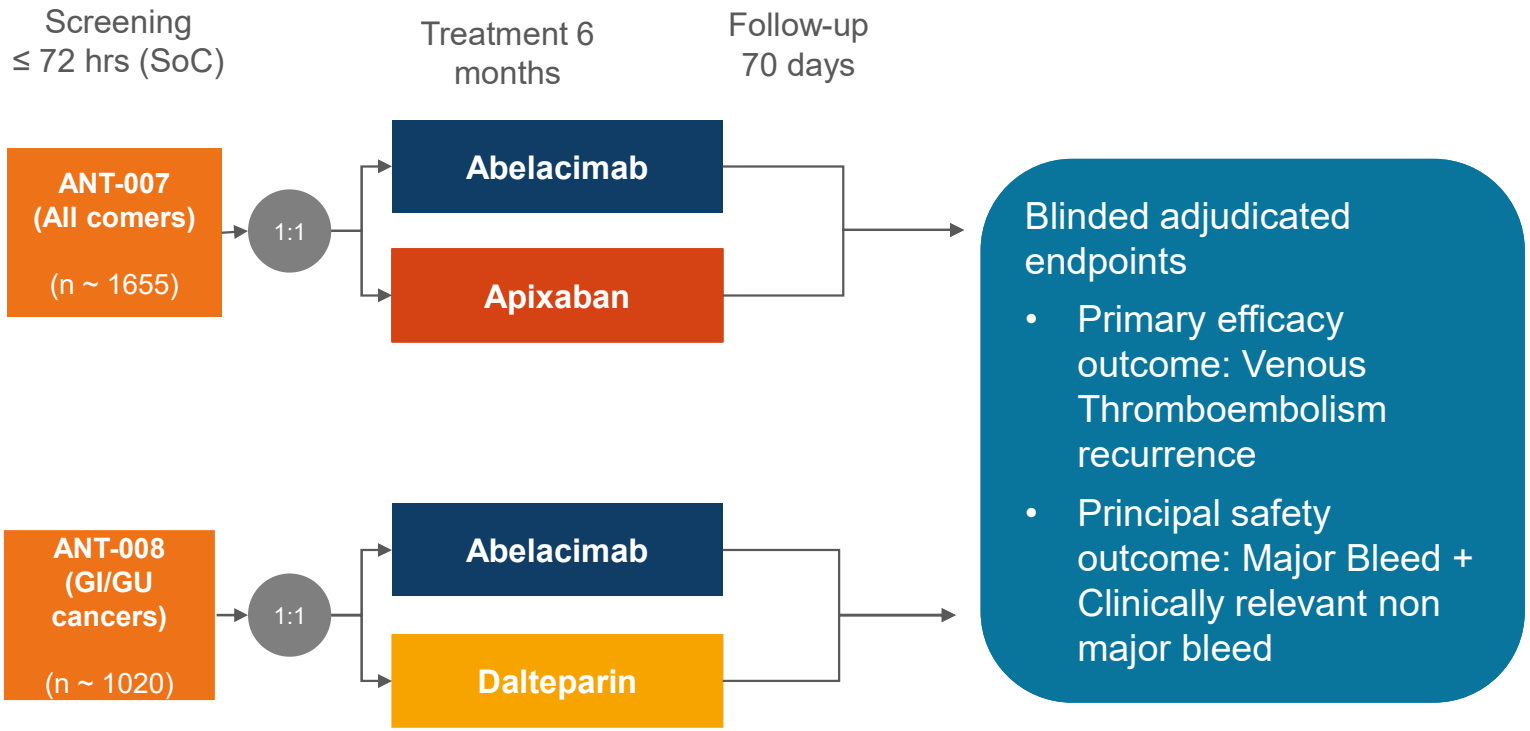
Table 2. Safety and Exploratory Efficacy Outcomes by Abelacimab (Pooled) Relative to Rivaroxaban Stratified by Creatinine Clearance (CrCl)

		Rivaroxaban[a]		Abelacimab (pooled)		Relative and absolute treatment effects for abelacimab (pooled) vs rivaroxaban			
Outcome	CrCl group	No./total No.	IR per 100 PY	No./total No.	IR per 100 PY	HR (95% CI)	*P* value interaction (HR)	ARR per 100 PY	*P* value interaction (ARR)
Major or CRNM bleeding	≤50 mL/min	20/87	13.6	11/176	3.5	0.26 (0.12-0.54)	.33	10.1	.09
	>50 mL/min	45/340	7.0	36/674	2.8	0.40 (0.26-0.62)		4.2	
Major bleeding	≤50 mL/min	11/87	6.9	4/176	1.3	0.19 (0.06-0.58)	.28	5.6	.09
	>50 mL/min	19/340	2.8	14/674	1.1	0.38 (0.19-0.75)		1.8	
Major, CRNM, or minor bleeding	≤50 mL/min	29/87	21.4	31/176	10.6	0.50 (0.30-0.83)	.55	10.8	.26
	>50 mL/min	82/340	13.8	100/674	8.3	0.60 (0.45-0.81)		5.5	
Stroke or systemic embolism	≤50 mL/min	2/87	1.2	4/176	1.3	1.03 (0.19-5.61)	.59	−0.049	.66
	>50 mL/min	5/340	0.7	17/674	1.3	1.77 (0.65-4.80)		−0.6	
Net clinical outcome[b]	≤50 mL/min	27/87	18.4	25/176	8.1	0.43 (0.25-0.75)	.26	10.3	.11
	>50 mL/min	64/340	10.1	81/674	6.3	0.63 (0.45-0.87)		3.8	

Abelacimab consistently reduced the risk of bleeding relative to rivaroxaban irrespective of kidney function

Patel SM, et al. JAMA Cardiol 2025

Design of the ANT-007 and ANT-008 studies



- DOACs are now Guideline recommended therapy in large subset of CAT patients
- Abelacimab may have safety and convenience advantages

- High unmet need:
  - High bleeding rate with DOACs
  - Dalteparin is still SoC in this subset of patients
- Abelacimab may have safety, efficacy and convenience advantages

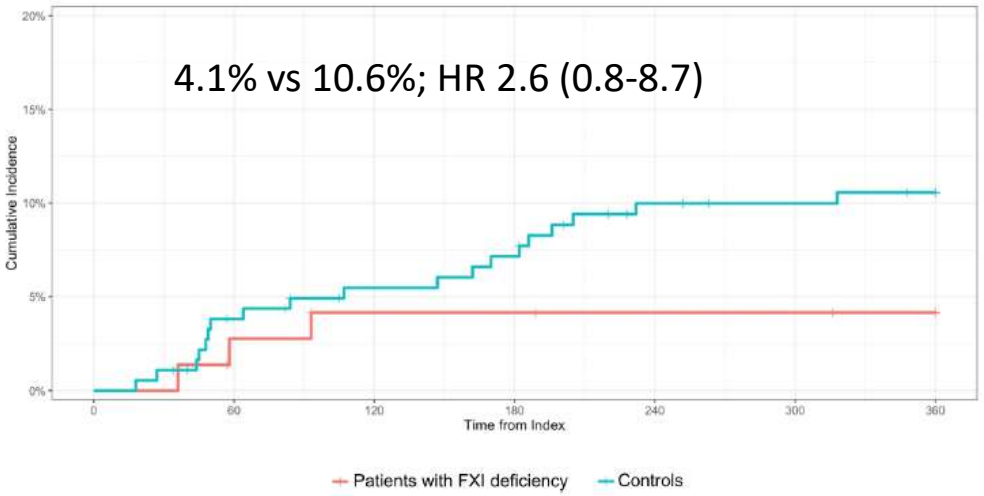
- Open-Label, Blinded Endpoint Evaluation
- Abelacimab 150 mg iv on Day 1 followed by abelacimab 150 mg sc every month
- Apixaban treatment: 10 mg bid for 7 days, followed by 5 mg bid in the ANT-007

  or
- Dalteparin 200 IU/kg/day sc from Day 1 to Day 30 then dalteparin 150 IU/kg/day sc in the ANT-008

VTE in patients with cancer and factor XI deficiency

Retrospective 73 cancer pts FXI deficient and 185 cancer pts with normal aPTT

Cumulative incidence of VTE at 12 mo



Bleeding at 12 mo in patients with FXI deficiency

Bleeding event	Absolute rate, % (n/N)	Cumulative incidence, % (95% CI)
Major bleeding		
All (within 12 mo)	15.1 (11/73)	15.0 (8.2-25.0)
Spontaneous (within 12 mo)[a]	4.1 (3/73)	4.4 (1.1-11.0)
Within 30 d after procedure/surgery[b]	8.6 (3/35)	8.6 (2.1-21.0)
CRNMB		
All (within 12 mo)	6.9 (5/73)	7.1 (2.6-15.0)
Spontaneous (within 12 mo)[a]	2.7 (2/73)	2.9 (0.55-9.2)
Within 30 d after procedure/surgery[b]	5.7 (2/35)	5.7 (1.0-17.0)

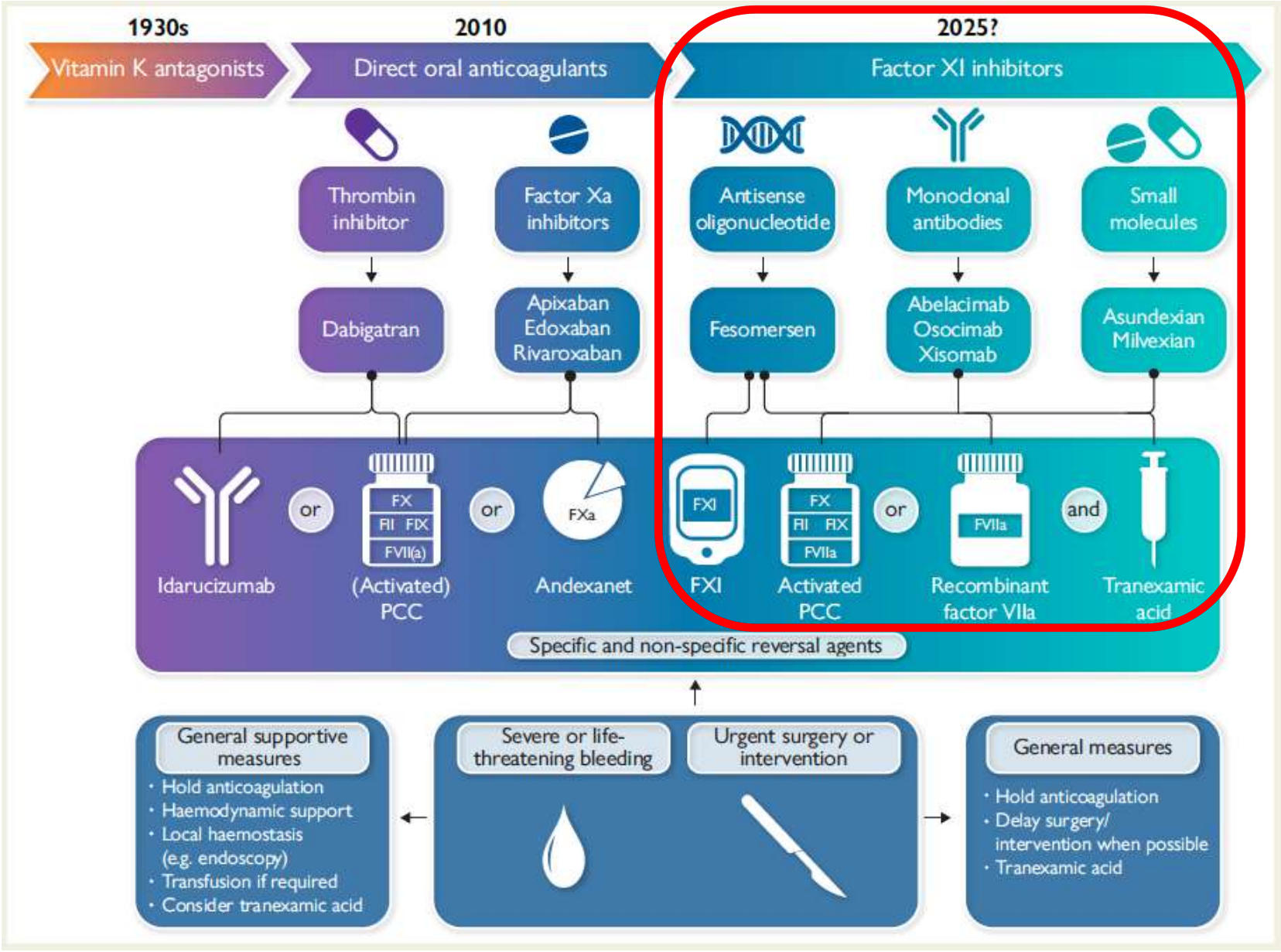
Controls:
MB 2.4%
CRNMB 2.3%

FXI deficiency was associated with reduced VTE risk in patients with cancer and increased bleeding expecially after surgery

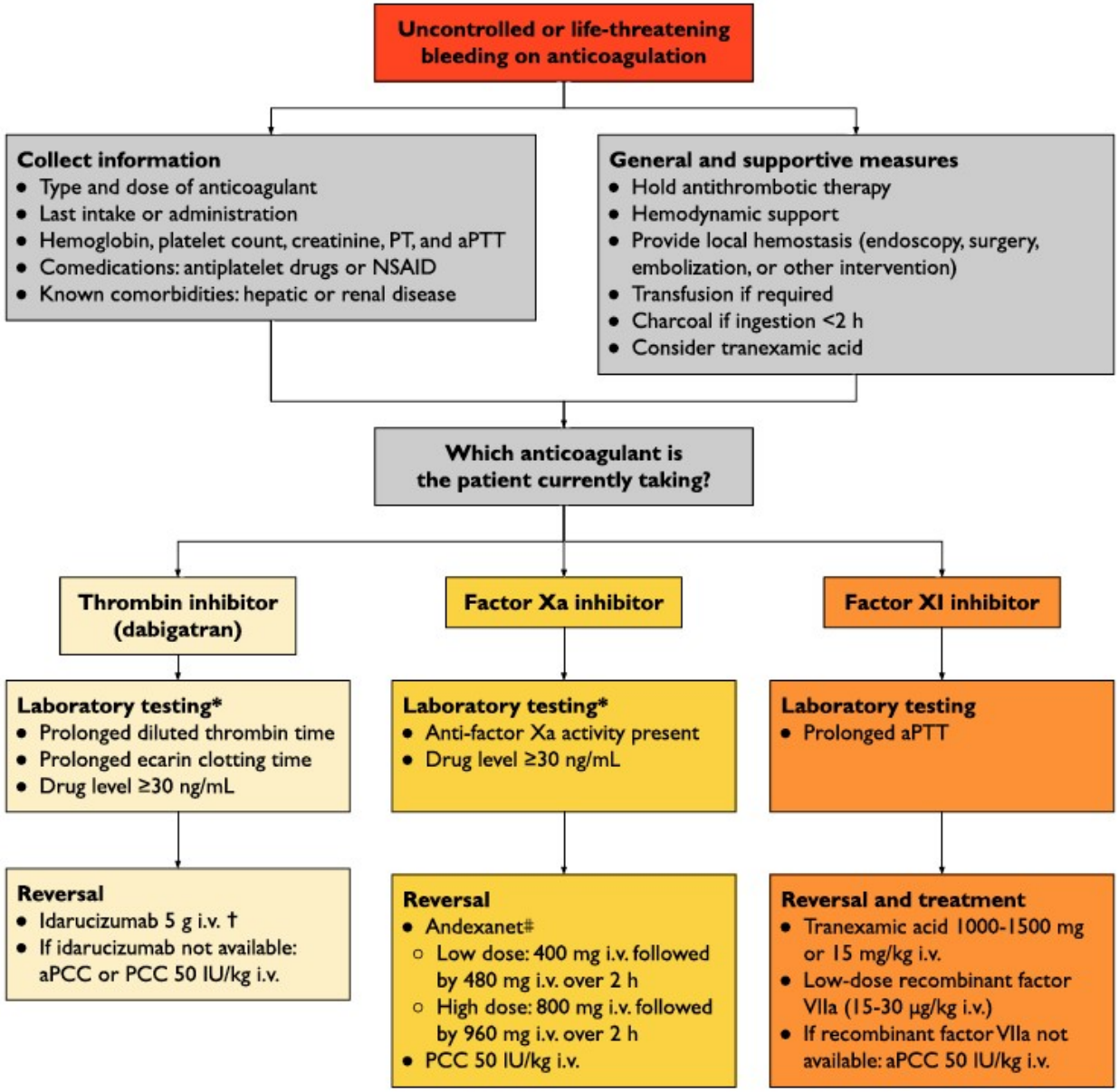
Chrysafi P, et al. JTH 2025

Outline

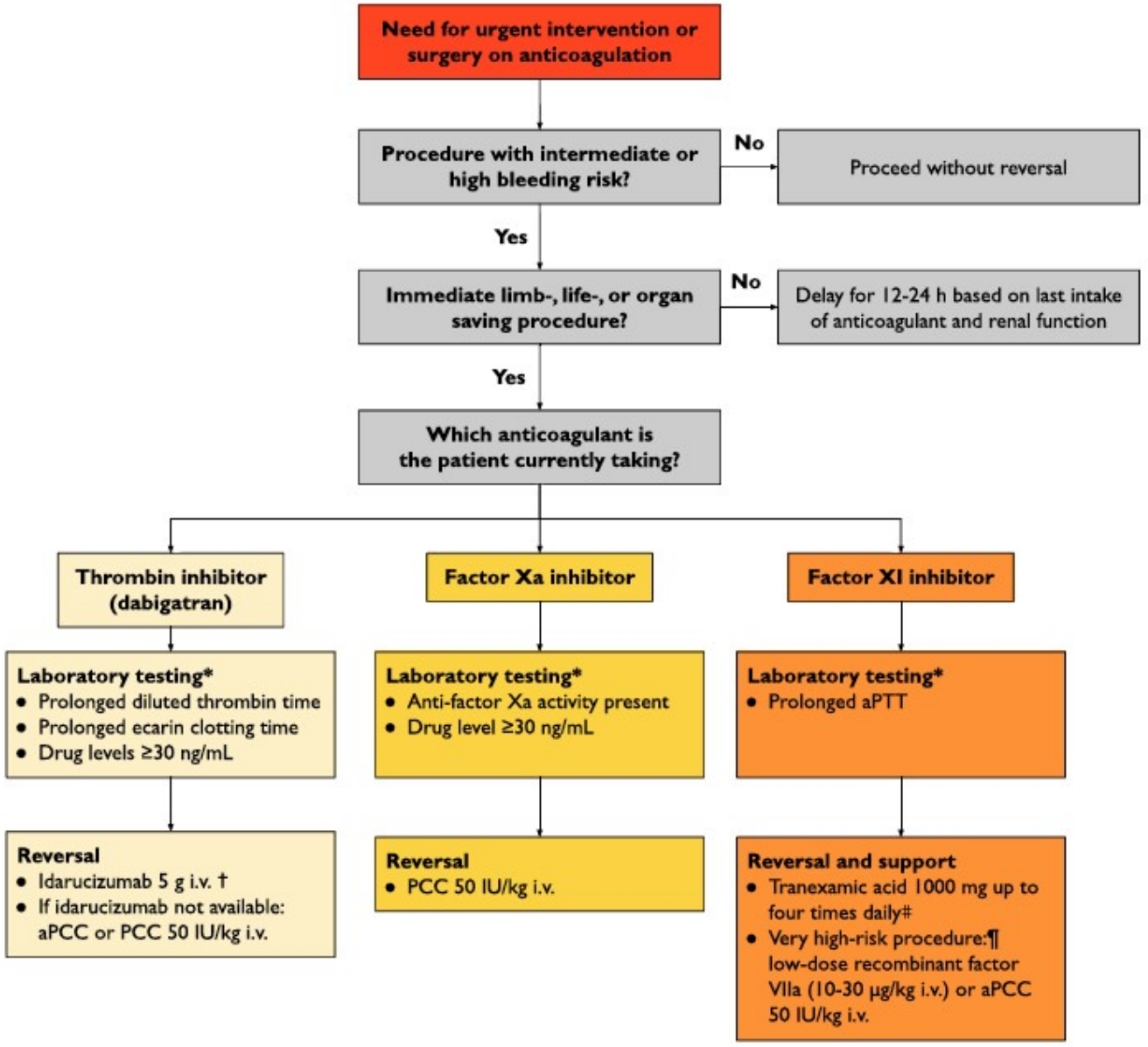
- Limitations of current anticoagulant treatments
- Role of FXI in hemostasis, thrombosis, and CAT
- Preclinical and epidemiological evidence supporting FXI as a safer target than FXa
- Clinical studies with FXI inhibitors
- Reversal agents and interference with coagulation assays
- Conclusions and future directions



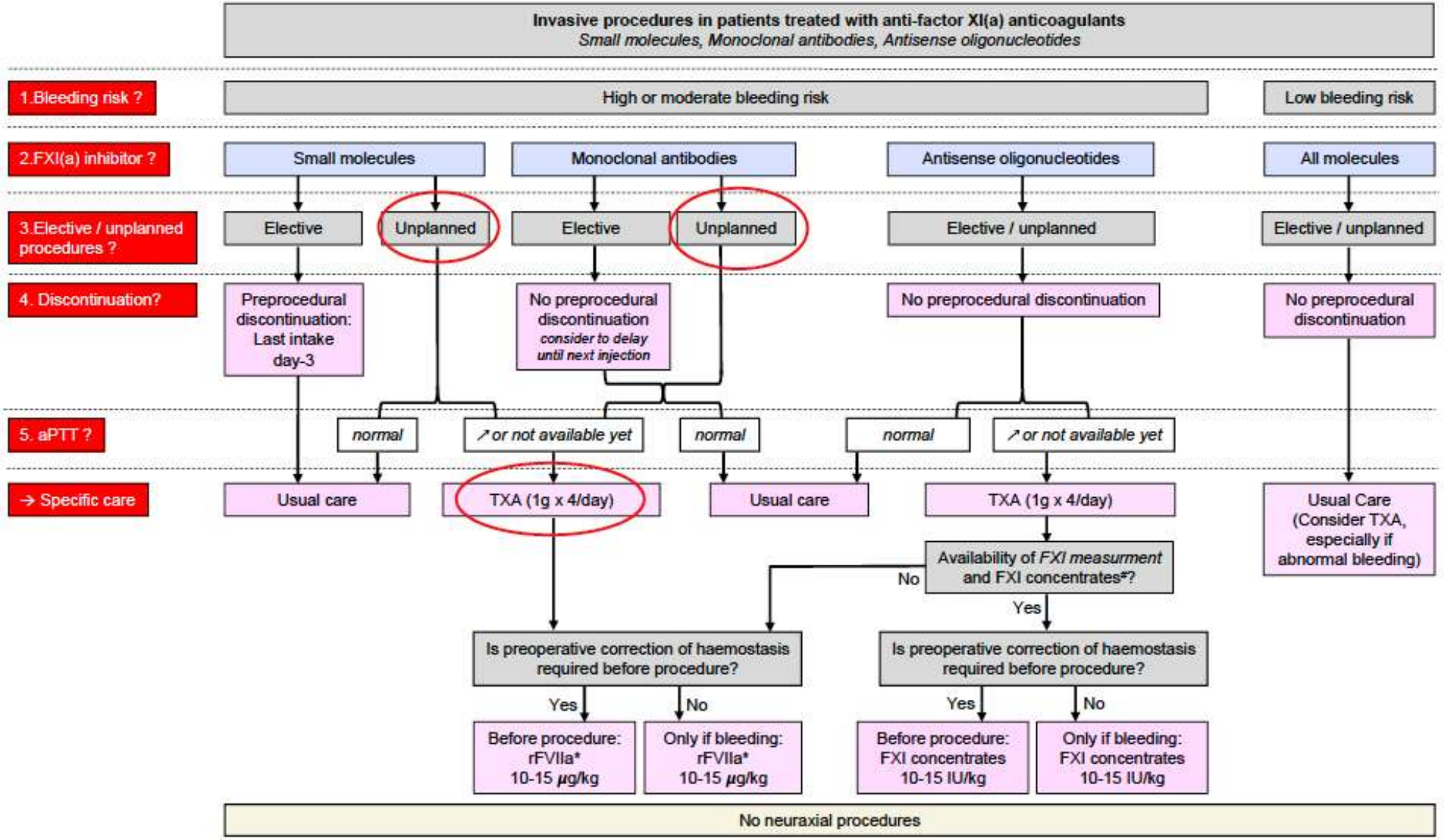
Van Es N, et al. Eur Heart J 2023



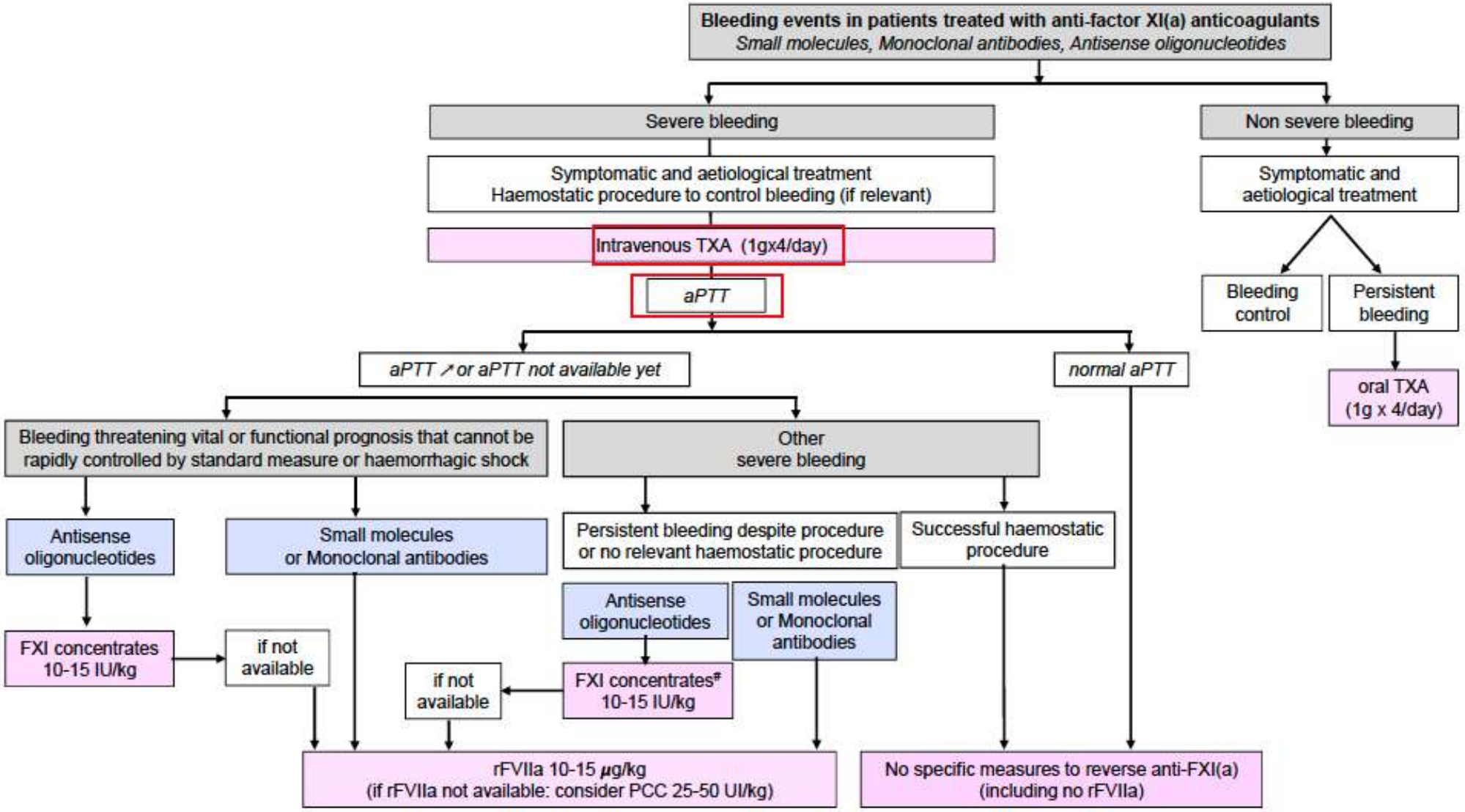
Van Es N, et al. Eur Heart J 2023



Van Es N, et al. Eur Heart J 2023



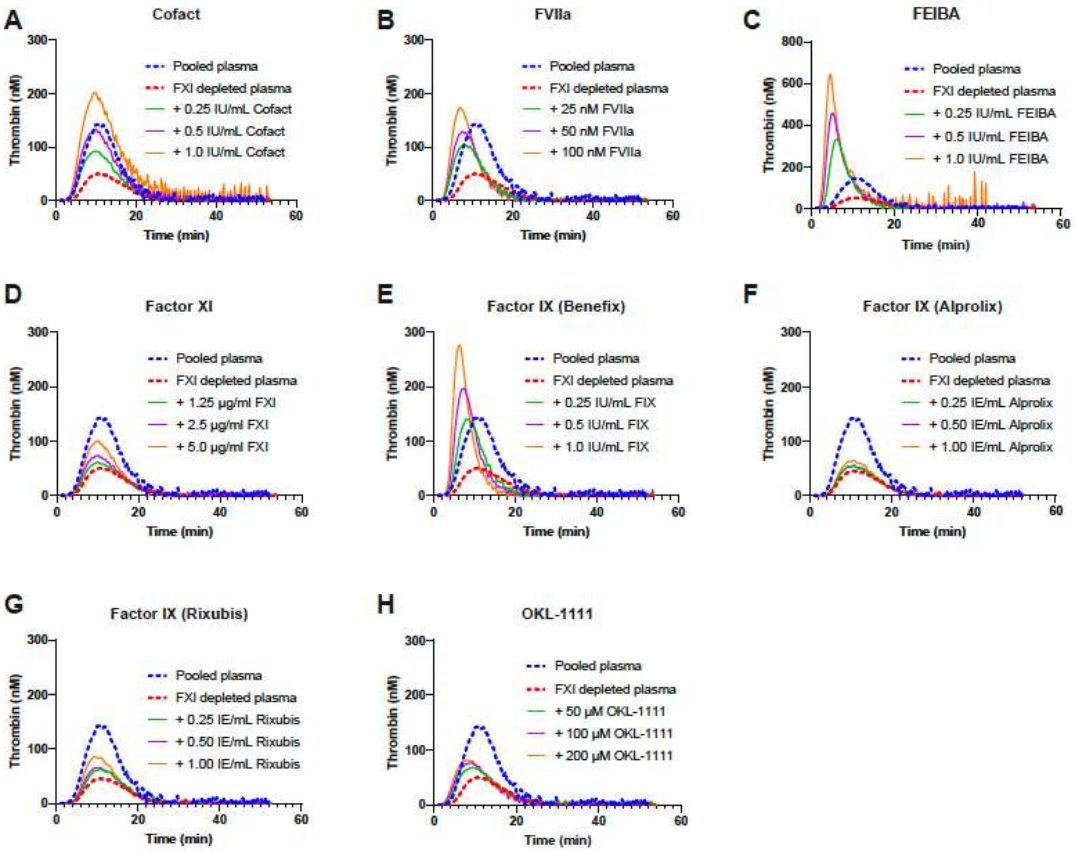
Godier A, et al. RPTH 2025



Godier A, et al. RPTH 2025

Reversal of factor XI targeting anticoagulants: an *in vitro* evaluation

FXI-depleted plasma as a model for fesomersen-treated patients

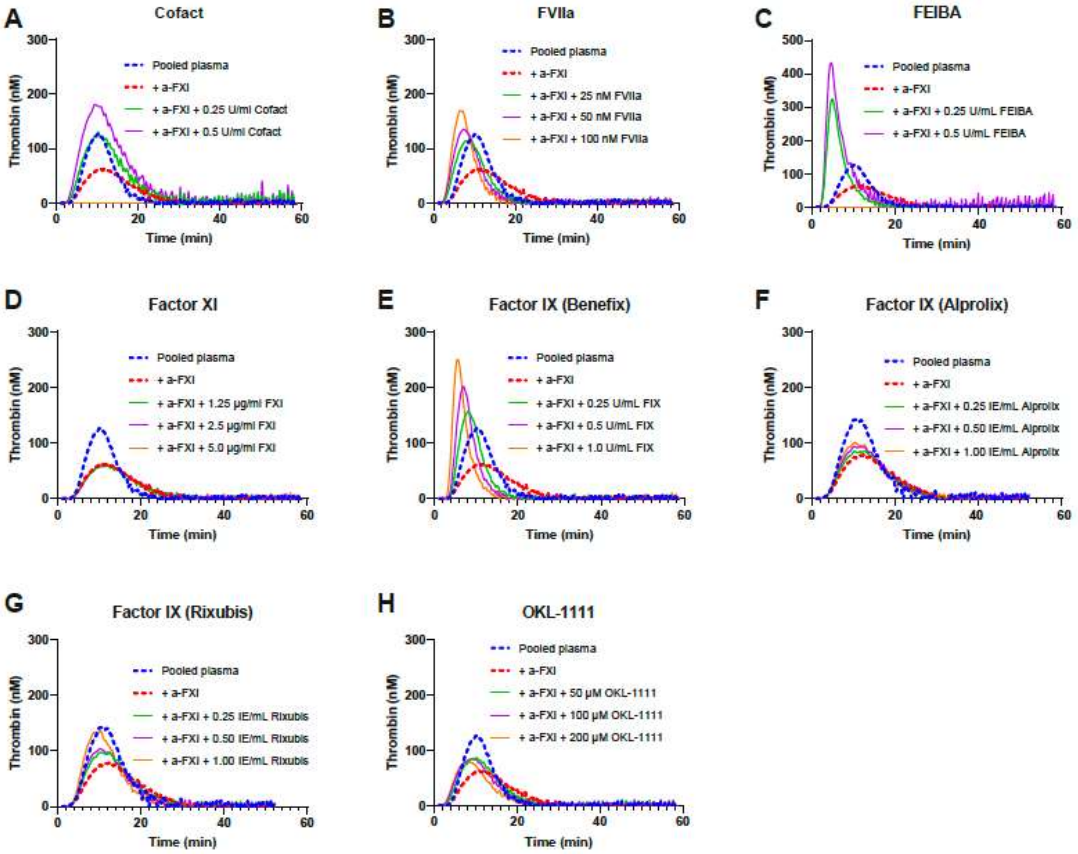


- ***Cofact, FEIBA and rFVIIa****: high thrombin generation*
- *FXI and OKL-1111 modest*
- *FIX very dependent on the origin of the protein (different content of FIXa)*

Bakhtiari K, et al. JTH 2023

Reversal of factor XI targeting anticoagulants: an in vitro evaluation

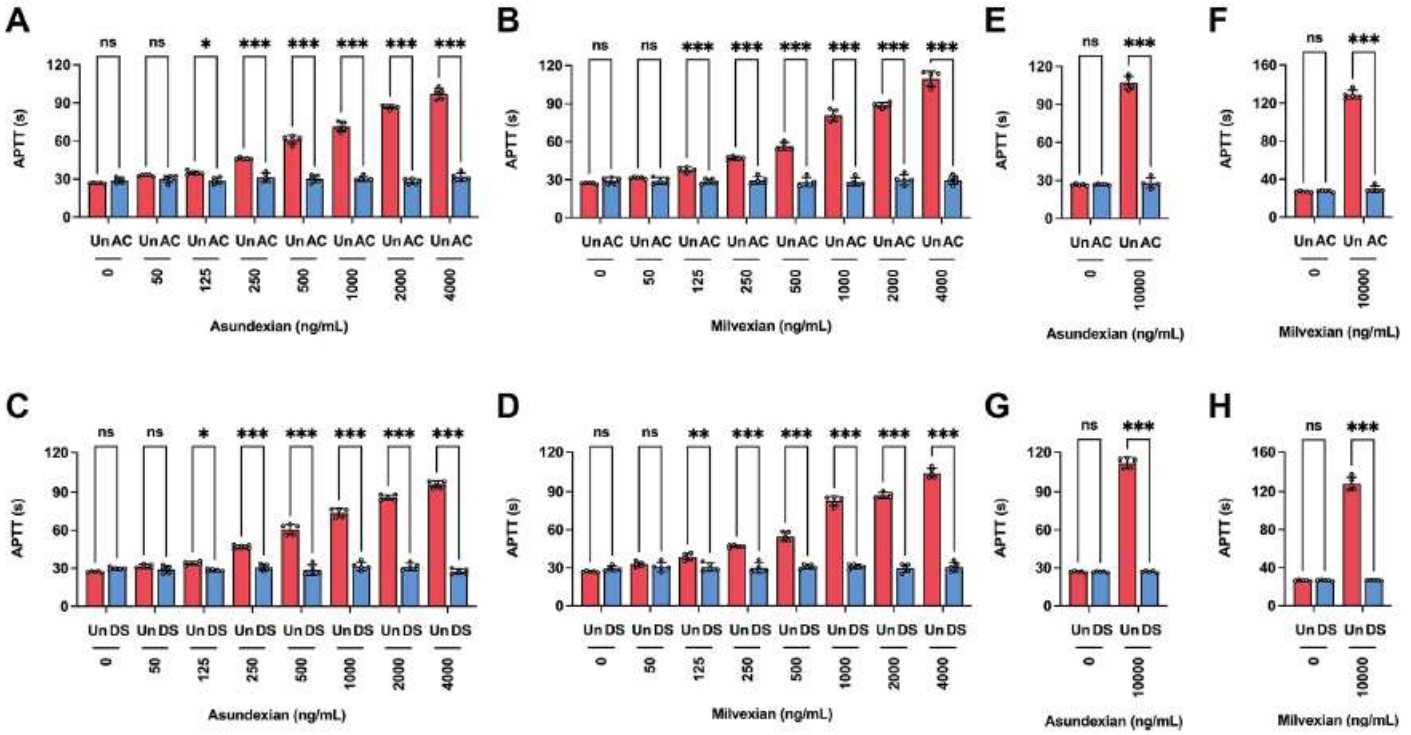
Normal plasma + inhibitory monoclonal antibodies as a model for other FXI targeting therapies



- ***FEIBA, Benefix, rFVIIa, Cofact****, and OKL-1111 enhanced peak thrombin levels*
- *Alprolix was not and Rixubus was less efficient*
- *FXI did not improve thrombin generation*

Bakhtiari K, et al. JTH 2023

Interferences with asundexian and milvexian in coagulation assays and their removal by activated charcoal-based adsorbents



Activated charcoal (blue bars)

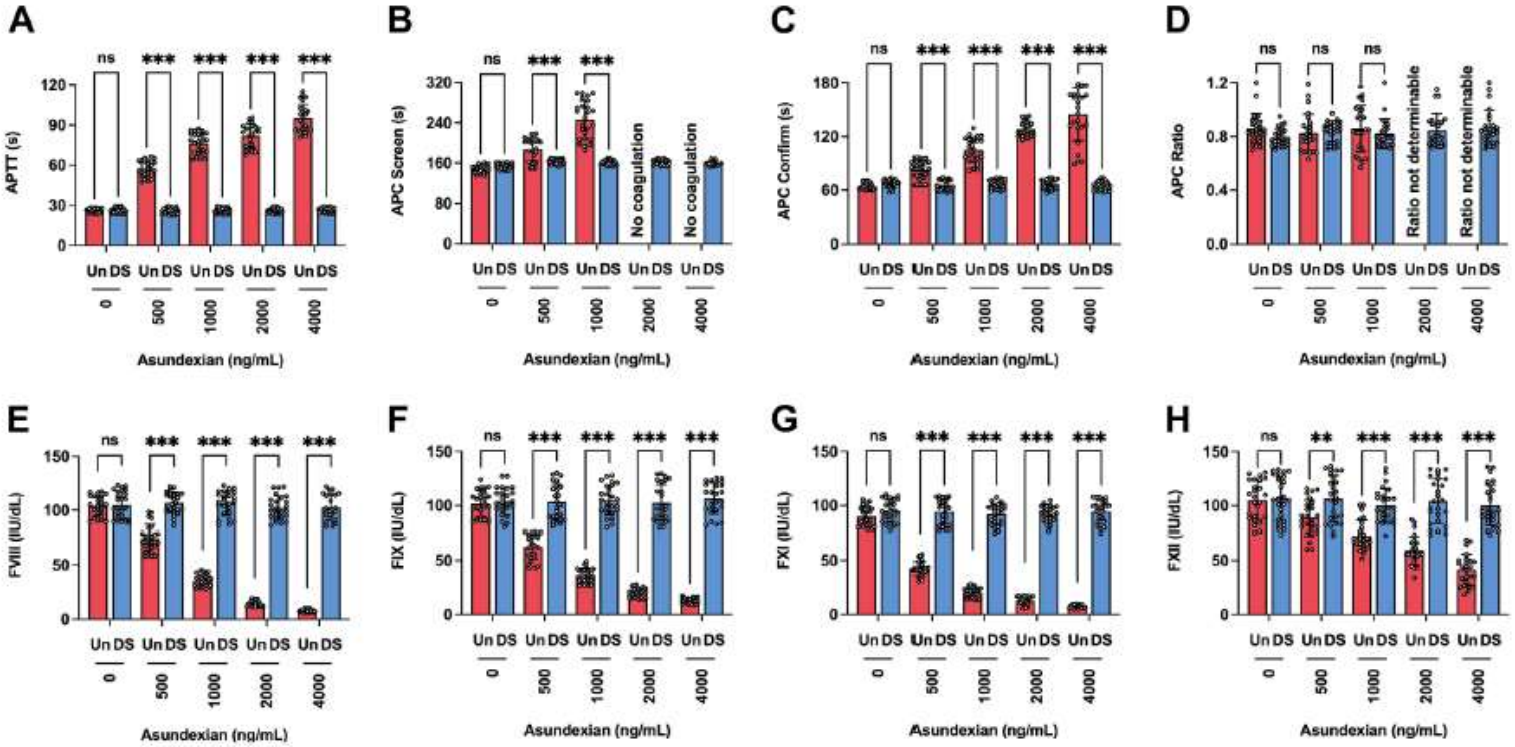
DOAC-Stop (blue bars)

Dose-dependent prolongation of APTT

Corrected by both activated charcoal (AC) and DOAC-Stop (DS), even for supratherapeutic concentrations (E/F and G/H)

Bucklery GT, et al. JTH 2025

DOAC-Stop: asundenxian

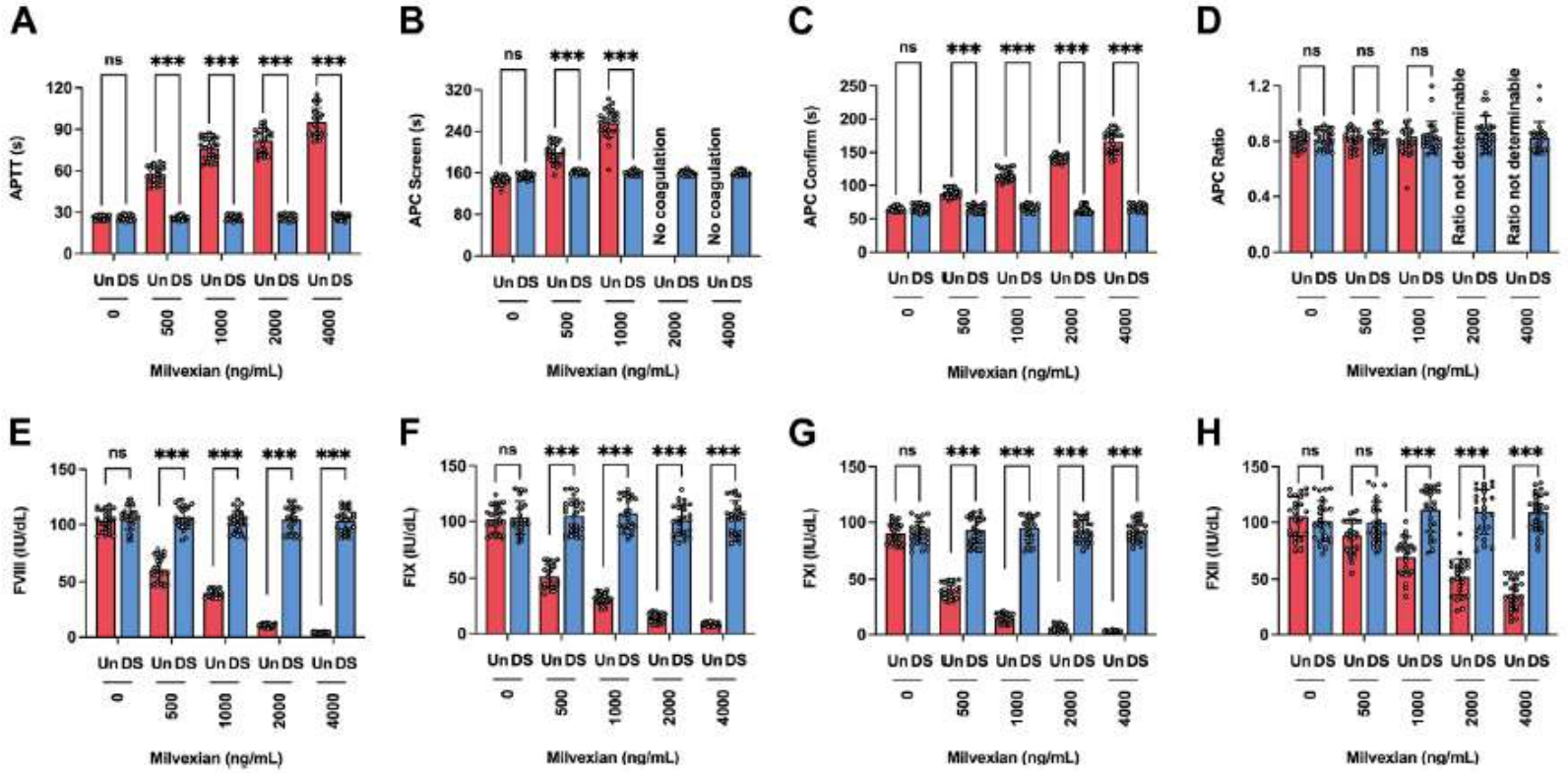


DOAC-Stop (blue bars)

- Dose-dependently reduced activities of FVIII, FIX, FXI, and FXII
- No appreciable interferences for FII, FV, FVII, FX, antithrombin, protein C, and protein S, the lupus anticoagulant, VWF:Ag, and the VWF activity

Bucklery GT, et al. JTH 2025

DOAC-Stop: asundexian



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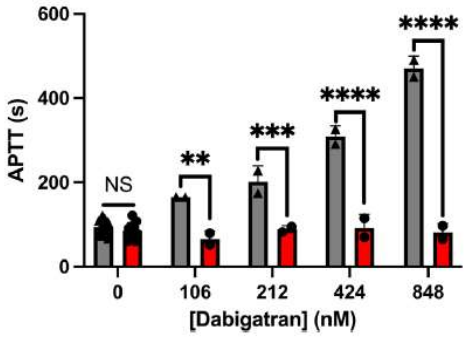
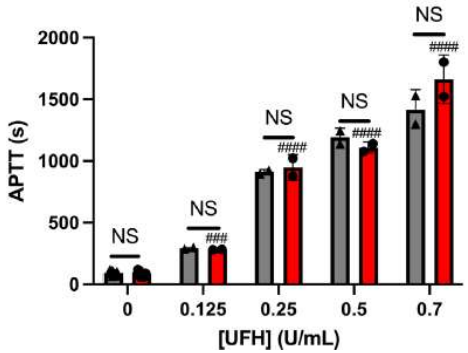
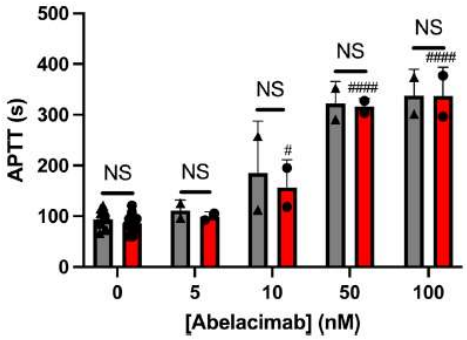
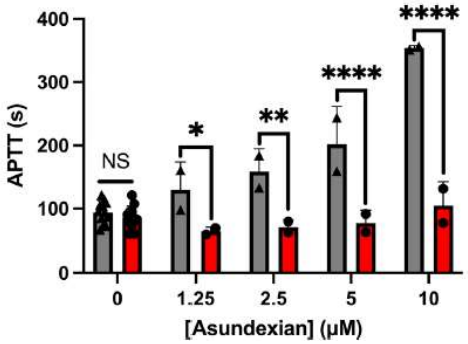
Bucklery GT, et al. JTH 2025

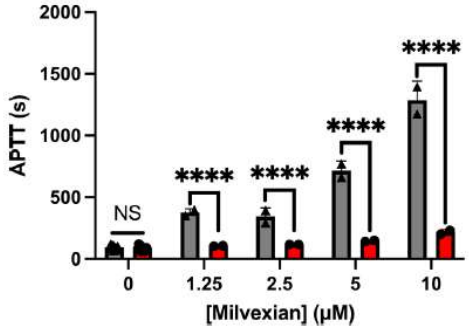


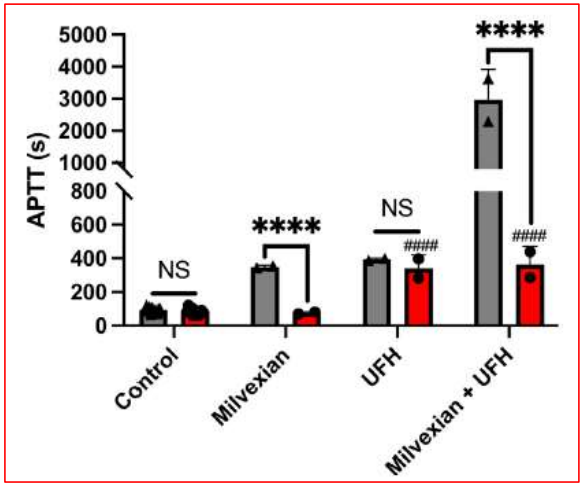




Red bars: DS-treated plasma





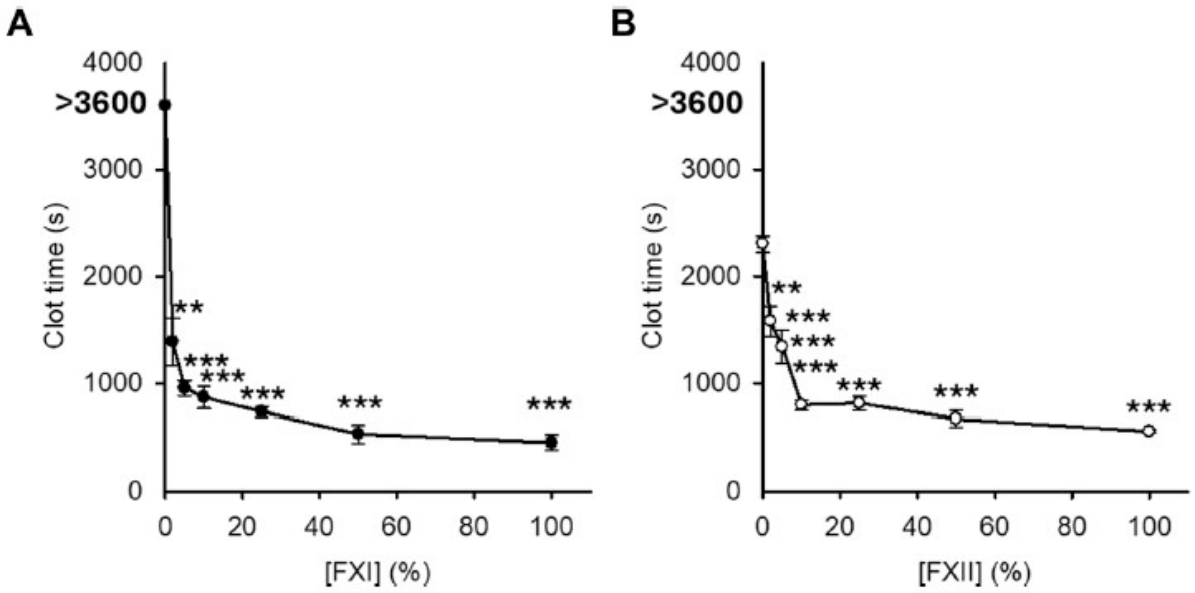


Dabigatran used as a positive control, while abelacimab and heparin served as negative controls

DOAC–Stop reverses the anticoagulant effect of asundexian and milvexian, not abelacimab or UFH, and distinguishes between the APTT effects of milvexian and heparin

Fitzpatrick EK, et al. JTH 2025

Milvexian alone or with heparin on catheter-induced clotting and thrombin generation

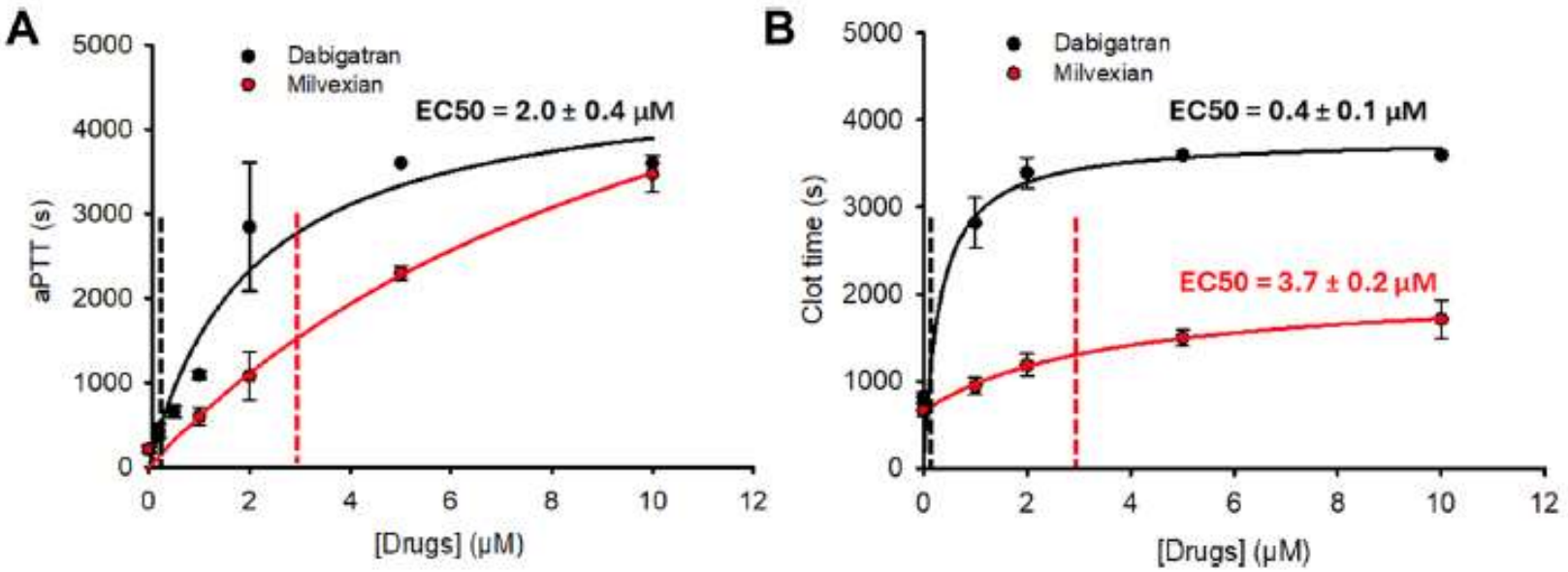


Clotting time was prolonged in FXII depleted and unmesurable in FXI depleted plasma

Repletion with <2% FXI or 5% FXII restored clotting times to approximately half of those measured with 100% FXI or FXII

Yin R, et al. JTH 2025

Milvexian alone or with heparin on catheter-induced clotting and thrombin generation

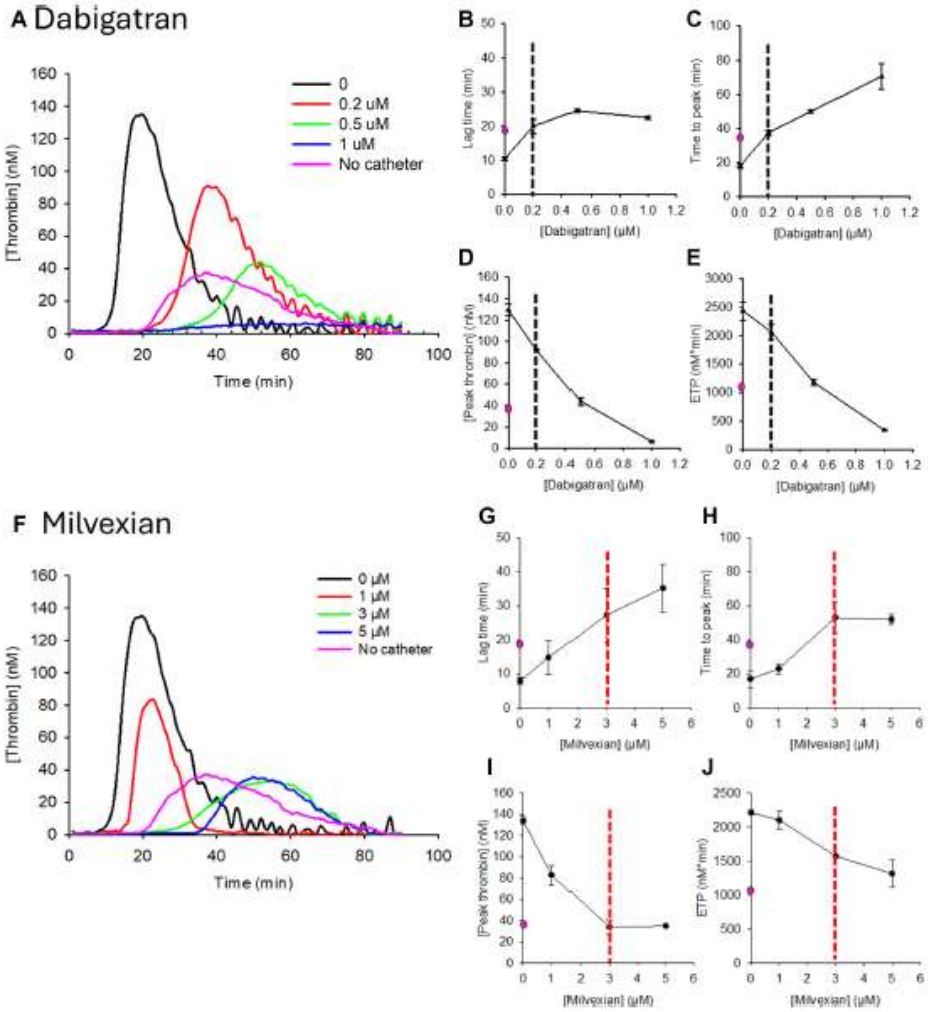


Compared with dabigatran, milvexian at therapeutic concentrations caused:

- greater aPTT prolongation
- lower clotting time prolongation

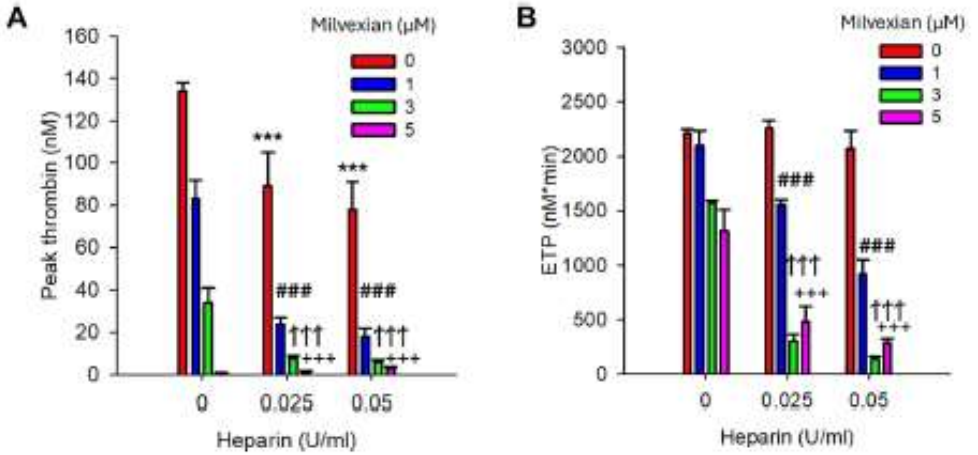
Yin R, et al. JTH 2025

Milvexian alone or with heparin on catheter-induced clotting and thrombin generation



At therapeutic concentrations, milvexian caused:

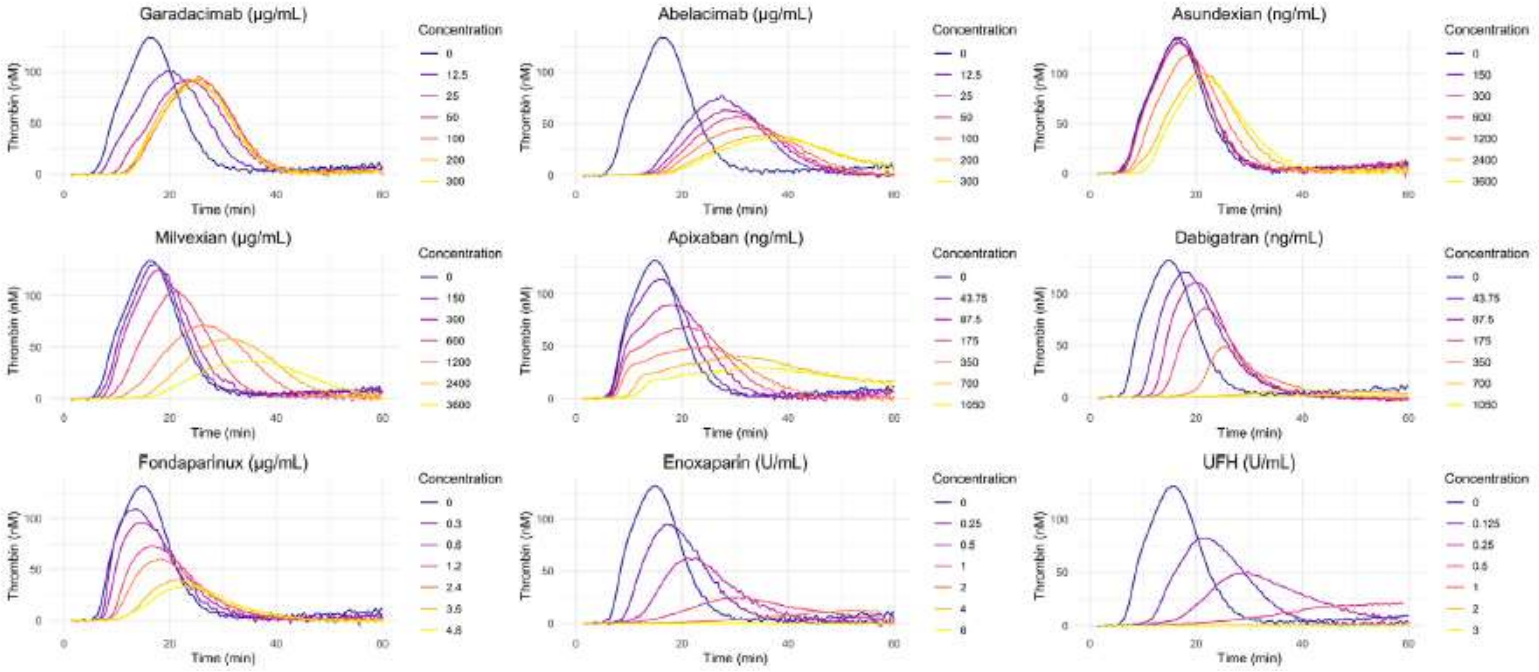
Greater effect on thrombin generation although this was not abrogated



Milvexian + heparin inhibit thrombin generation in a more than additive manner

Yin R, et al. JTH 2025

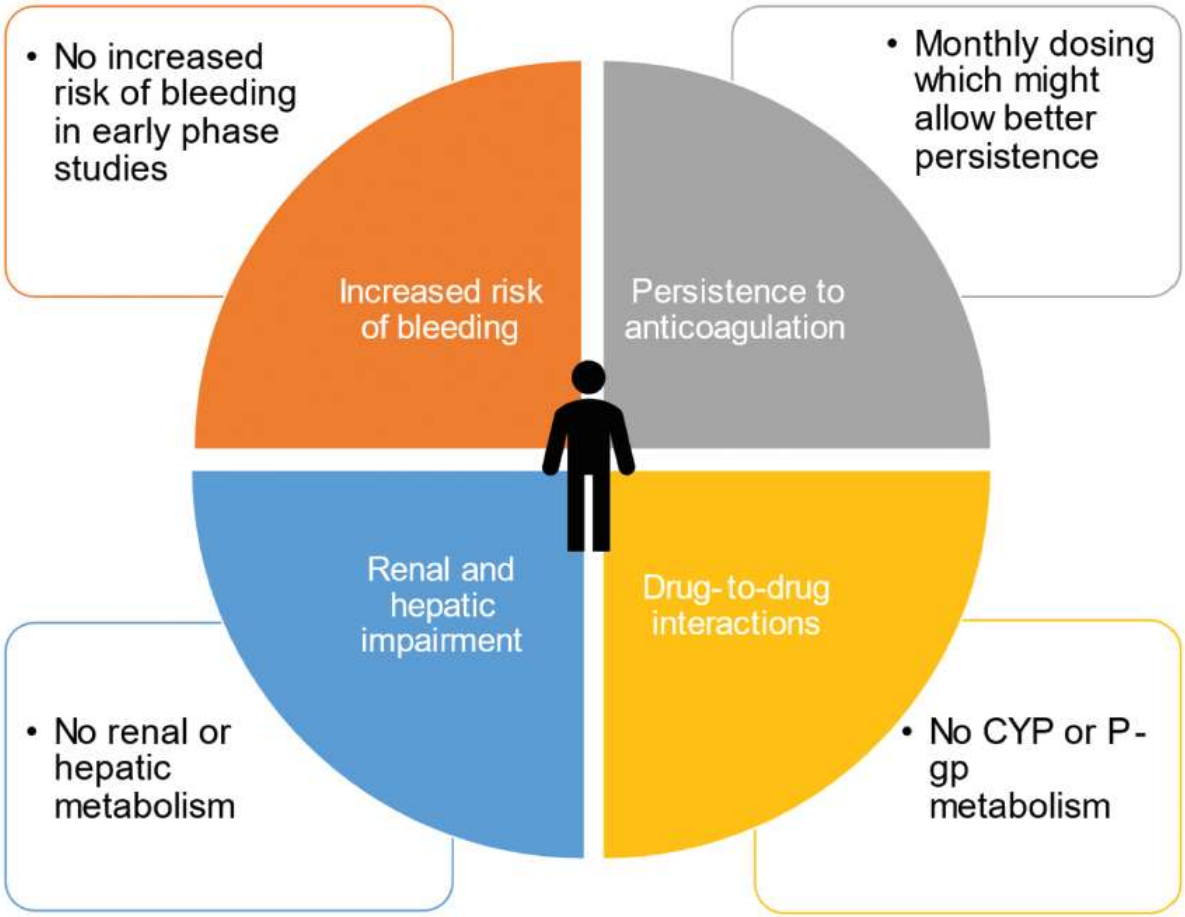
Effect of heparins, direct oral anticoagulants, and factor XII/factor XI inhibitors on catheter-initiated thrombin generation in platelet-rich plasma: an in vitro study



- **UFH was the only anticoagulant capable of suppressing thrombin generation at concentrations compatible with clinical care**
- FXIIa and FXI(a) inhibitors were less effective than UFH or LMWH
- DOACs and fondaparinux showed limited efficacy

Hardy M, et al. JTH 2025

Limits of current anticoagulants for CAT and how factor XI inhibitors could address these issues



Wang T-F, et al. The Oncologist, 2023

Conclusions

- FXI is emerging as a promising target for new anticoagulants
- Several FXI inhibitors are under clinical investigation
- Phase 2 studies of FXI inhibitors suggest a good safety profile
- Phase 3 next critical step to determine actual benefit-risk of FXI inhibitors in AF/VTE
- Abelacimab is the only FXI inhibitor that has advanced to phase III evaluation in CAT

Factor XI: A new target for anticoagulation?

Dr. Marcello Di Nisio

University G. D'Annunzio , Chieti-Pescara, Italy